VOLUME 104 • SEPTEMBER 1959 • NUMBER 3

ARCHIVES OF INTERNAL MEDICINE

A Biased Guide to Renal Hypertension
Prof. W. S. Peart

Evaluation of the Adequacy of Needle-Biopsy Specimens of the Kidney
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Chlorpropamide in the Management of Diabetes
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Penicillin Sensitivity of Gram-Negative Enteric Bacilli
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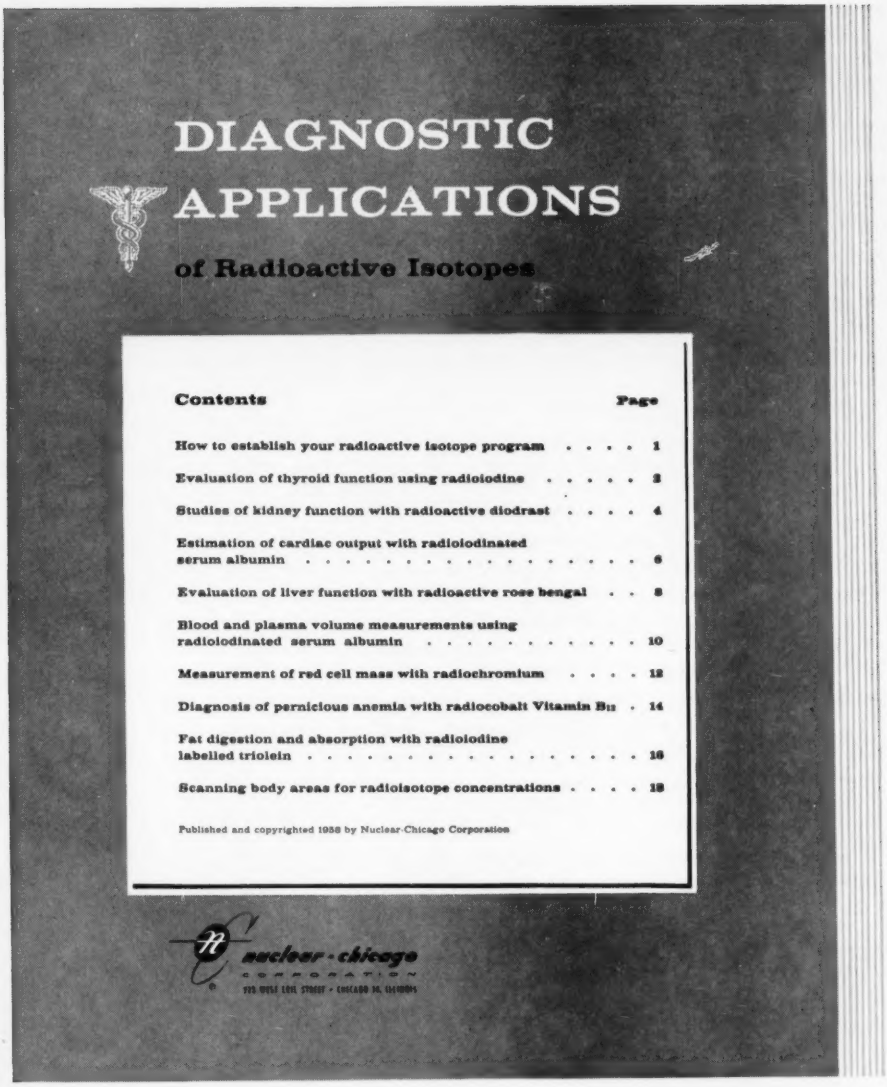
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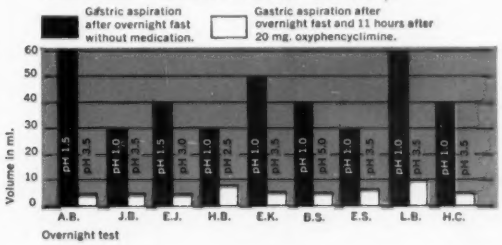

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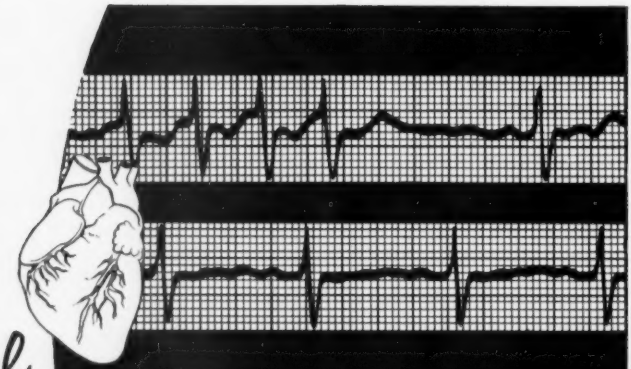

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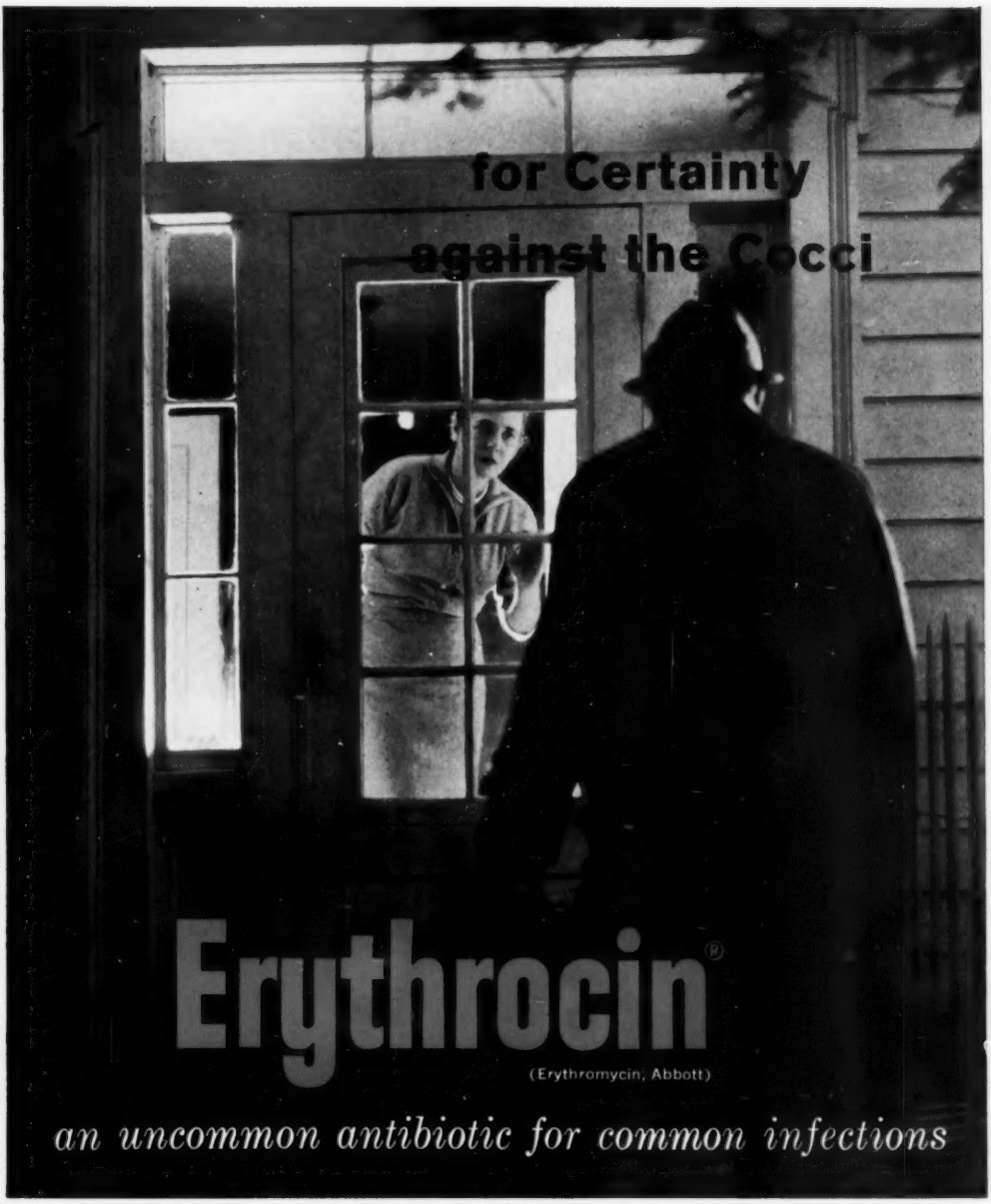

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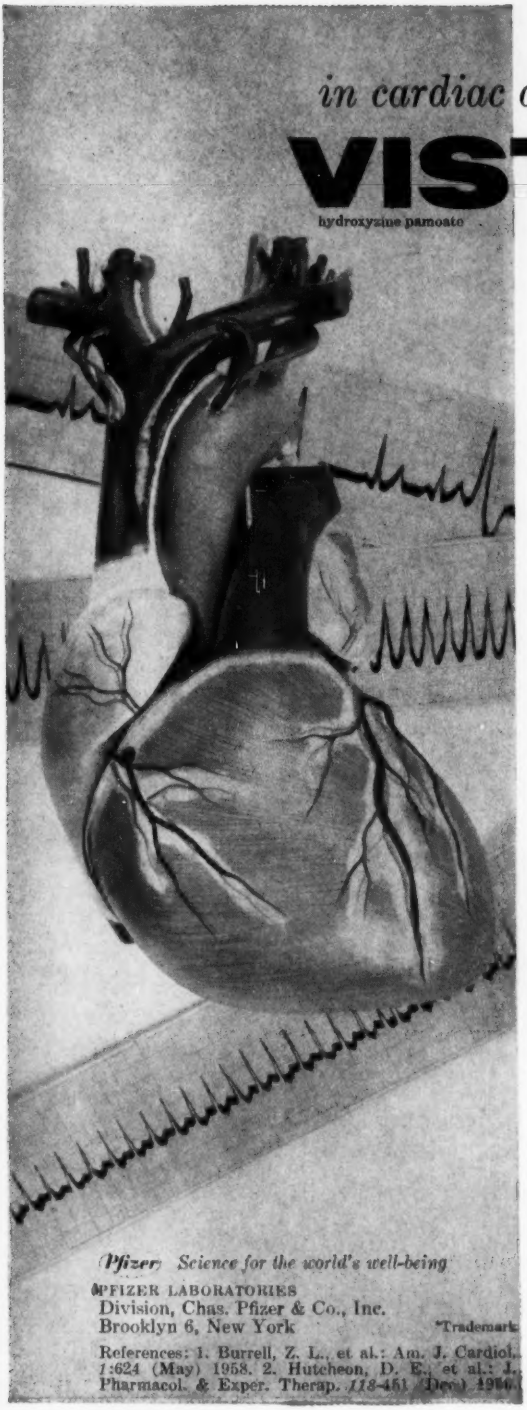

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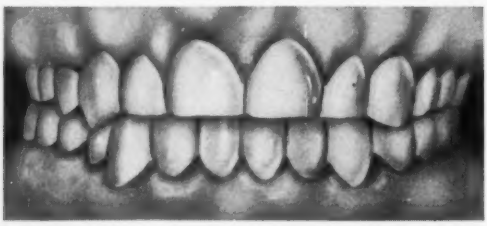

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A.M.A. ARCHIVES OF
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Editorials

A Biased Guide to Renal Hypertension

To the uninitiated looking into the field of hypertension due to renal causes—and of course to many there is no other form of hypertension—there is presented a bewildering prospect. This is made worse by each succeeding conference, for within the published proceedings of such conferences (Circulation 17:2, 1958) each clear statement about the mechanism of hypertension, both human and experimental, seems to be balanced by a contradictory one. Going further into the subject and reading the evidence might cause further bemusement, since what is said here is said in hundreds of voices instead of the one at the conference. Why is it that the field of hypertension is so confusing? I believe this state has arisen for a number of reasons which are worth considering, and I should like to present here a highly biased guide to the field.

Some of the main ways in which the kidney could participate in hypertension are (1) failure to excrete or destroy an extrarenal pressor substance; (2) failure to produce a vasodilator; (3) increased responsiveness of normal pressor mechanisms; (4) decreased response of baroreceptors; (5) stimulation of some extrarenal pressor system, e. g., the adrenal; (6) redistribution of electrolytes and water, and (7) production of a vasoconstrictor. I wish to make some sweeping statements to cover certain of these categories where I think the evidence is inconclusive or indicates what may be termed a permissive function and not a causal one, and I have selected the most important findings for discussion.

It is an old dictum in biological circles that results obtained in one animal may not apply in another. There are few statements to which so much lip service and so little practical regard are given in the field of hypertension. This must therefore be constantly borne in mind in considering the evidence, for example, the fact that man is, with the rat, unique in that interference with one kidney leads to hypertension even if the other normal kidney is left intact.

Possible Role of Kidney in Hypertension

1. *Failure to Excrete or Destroy Extrarenal Pressor Substance.*—It is clear that in man this is not in itself a sufficient explanation, since hypertension does not occur necessarily in anuria due to many causes (e. g., septic abortion) even if this is prolonged up to three to four weeks (personal experience; Bull, Joekes, and Lowe, 1955), and this is probably true in much experimental hypertension, though failure of excretion is common in these situations and may influence the course of the hypertension.

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This raises the question of what is different about the kidney in one form of anuria, tubular necrosis, compared with the anuria of acute glomerulonephritis. In the former, hypertension is uncommon; in the latter, of course, hypertension is characteristic. The particular function of the kidney that is different in these two situations is one of the main points about which more information is needed. The most crucial human observation made is that of Murray, Merrill, and Harrison (1958), who showed that in certain of their kidney transplantations in identical twins the blood pressure was lowered to normal by the transplant with the diseased kidneys still remaining and was not further lowered by their subsequent removal. It is hard to believe that this represented, for example, removal of a circulating vasoconstrictor, and yet there are other human situations where the presence of a normal kidney is not sufficient to prevent hypertension. I refer, of course, to unilateral renal disease of various sorts, including pyelonephritis and renal artery stenosis. There the question must be: What is the difference that makes normal renal tissue ineffective? Immediately then it is clear that there must be more than one mechanism at work, and those who find pleasure in a single, all-embracing hypothesis are saddened.

2. *Failure to Produce a Vasodilator.*—This is a favorite view of Grollman's for which I think the evidence is still tenuous (Hamilton and Grollman, 1958).

The first and second postulates taken together cover the idea that the hypertension produced by removal of the kidneys, renoprival, is the main state called into action by most forms of interference with the kidney, though what this state is has so far defied definition. This word renoprival is in danger of representing a unified explanation when, from what has been said already, it is clear that there must be many different states included under its head.

3. *Increased Responsiveness of Normal Pressor Mechanisms.*—These have often been discussed but never adequately measured, and it should be noted that there has been no convincing demonstration of increased sensitivity to any natural substance in renal hypertension. The word sensitivity is often misused in the sense that if a patient responds by a greater rise of blood pressure to an injection of, for example, norepinephrine, this is claimed to mean increased sensitivity. The diameter of the arterioles in hypertension is smaller than normal, since the peripheral resistance is elevated, and therefore it would be expected that constrictor drugs would have a greater effect. This use of the term sensitivity, which implies an alteration in the response of smooth muscle, should not be lightly accepted without better evidence (Ogden, Brown, and Page, 1940; Duff, 1957, and Conway, 1955).

4. *Decreased Response of Baroreceptors.*—That they must alter in response to any form of hypertension is self-evident; otherwise there would be no hypertension, and in man they have always seemed to be poor regulators of pressor effects. The most significant experiment here is that of McCubbin, Green, and Page (1956), who showed that in the dog with renal hypertension the baroreceptors certainly adjusted rapidly to the higher pressure.

5. *Stimulation of Some Extrarenal Pressor System.*—The possibility that the kidney might release a substance which directly stimulated some such system received support when Goldblatt (1937) showed that adrenalectomy lowered the blood pressure of the dog with renal-artery-clamp hypertension. I believe that the adrenal only serves a permissive function and has not a causal role. The relative failure of adrenalectomy to relieve hypertension in man supports this,

as also does the clear demonstration by Fregly (1957) that it is possible to develop hypertension by clamping the renal artery in adrenalectomized rats. It may be more important in the dog, however.

6. *Redistribution of Electrolytes and Water.*—In this field I think nothing has been shown that may not occur as a result of the hypertension, and despite changes in arterial wall electrolytes (Tobian and Redleaf, 1958) and in the excretion of sodium and water by the kidney (see Sapirstein, 1957, for references), it is significant that the latter changes can be reversed by returning the blood pressure to normal by either sympathectomy (Thompson et al., 1954) or hypotensive drugs (Hollander, 1958). This observation should be extended to vessel wall electrolyte changes also.

7. *Production of a Vasoconstrictor.*—After 1898, when Tigerstedt and Bergman discovered renin in the kidney and defined most of its characteristics, there was a fallow period until the "memorable experiment" of Goldblatt et al. (1934), who demonstrated the renal-artery-clamp hypertension. Attempts to link these two observations have continued ever since, and the present situation is undoubtedly one of confusion. To make my position clear, I must state that I do not think there is good evidence for a physiological or pathological role for renin in controlling the blood pressure. Why is it that for the past twenty-five years controversy has raged about this subject? Firstly, the outstanding fact in the literature is that workers have forgotten that renin is not a pure substance as usually used and should properly be written "renin." It is common in research work, unfortunately, for an effect to be given a name as if it were a pure substance, and so all similar effects are then given this name and the idea of reality and of error starts. This is the case with "renin" and "angiotensin" (hypertensin or angiotonin, Braun-Menéndez and Page, 1958). Before any worker claims to have shown the presence of renin or angiotensin in a biological fluid, I suggest he should be able to satisfy the following criteria, which are common in protein or peptide studies, and if such criteria are applied to most published work the claims are seen in their true light, as unsubstantiated by reasonable evidence.

A. Renin
   1. The form of the pressor effect should be identical with standard renin.
   2. Activity should be lost by heating.
   3. The ability to make angiotensin should be demonstrated.

B. Angiotensin
   1. The form of the pressor effect should be identical with pure substance.
   2. (*a*) Action on other test objects should be the same as the pure substance.
      (*b*) There should be identity of behavior with the pure substance with use of different methods of physical separation.

The ways in which artifacts with similar appearance and effect to renin and angiotensin appear in blood taken from the circulation in man and other animals are notable in my experience. To reduce the evidence to the barest essentials, there are two main lines of evidence as to the participation of renin and angiotensin.

1. Direct: Claims have varied from failure to success in the demonstration of renin in the circulation (Braun-Menéndez et al., 1946; Merrill, Morrison, and Brannon, 1946, and Haynes, Dexter, and Seibel, 1947), and the evidence of those claiming success must be looked at with care. Robertson and I (1958, unpublished) have obtained renal vein blood from both kidneys in patients with malignant hypertension, often due to unilateral renal disease, including renal

artery stenosis, with use of a guided-tip catheter (Peart and Sutton, 1958). Comparisons could therefore be readily made, and we were unable to show the presence of renin by use of an assay we believed to be adequate, since it would have served to show the presence of angiotensin infused at a rate which we have found sufficient to cause definite hypertension in man. It would then have to be argued that the patients were more sensitive to smaller quantities or that other factors were maintaining the hypertension in addition. Similarly, we examined the hypertension of renal artery clamping in the rabbit and were unable to demonstrate renin at any stage of hypertension, early or late, though we could readily show it in the blood when renin was infused to give hypertension of a comparable degree to the renal artery clamping. This contrasts with the two main pieces of evidence about renin and angiotensin claiming their presence. Kahn et al. (1952) claimed that patients with malignant hypertension had up to twenty times any normal amount of hypertensin in their blood, and Gollan, Richardson, and Goldblatt (1948) and Skeggs, Kahn, and Shumway (1951) made a similar claim in the dog with renal-artery-clamp hypertension. I think there is insufficient evidence that angiotensin was the substance which was present. In these situations the evidence should be made more definitive so that confusion may be brought to an end.

2. Indirect: This has mainly concerned antirenin, first introduced by Johnson and Wakerlin (1940). There seems no doubt that serum capable of antagonizing renin in vitro is capable of lowering the blood pressure of dogs with renal-artery-clamp hypertension, but I feel that indirect evidence of this sort is always liable to the unsuspected variable, and it should be pointed out that these pharmacological effects may not be due to antirenin alone, since the sera are not pure substances and their mode of action must still be regarded as incompletely understood. Such sera prepared from pure renin may provide a more complete answer.

There is other indirect evidence which requires notice. Since the isolation and amino acid sequence of angiotensin peptides was accomplished (Peart, 1955; Elliott and Peart, 1956; Skeggs et al., 1955 and 1956), synthesis soon followed (Schwyzer and Sieber, 1956; Bumpus, Schwarz, and Page, 1957). It then became possible to study their actions more readily. By use of such synthetic angiotensin in man, Pickering, Sanderson, and Peart (1958, unpublished) and Bock et al. have shown that, for example, the skin flow is reduced and, more important, urine flow is very markedly reduced, as is electrolyte excretion. Now in most patients with hypertension, the skin flow is within normal limits and the output of sodium and water is elevated (see above). Readjustment of the circulation would therefore be necessary, especially with respect to the kidney, and the action of angiotensin would have to be modified in the chronic state compared with the acute experiment.

Over all, in the field of renin and hypertensin I feel that the onus of better proof is on those who claim its presence. The present confusing situation would not have arisen if reasonable criteria of their presence had been followed.

The picture of the kidney in hypertension then is one of many possible roles and almost certainly of a variety of ways in which the blood pressure may be raised when it is diseased or otherwise interfered with.

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Evaluation of the Adequacy of Needle-Biopsy Specimens of the Kidney

An Autopsy Study

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Percutaneous needle biopsy of various organs and tissues has become a useful and important diagnostic procedure. Since the report by Iversen and Roholm,[1] in 1939, needle biopsy of the liver has been accepted as a reliable technique for demonstrating structural changes which occur in diseases of this organ.

In 1951, Iversen and Brun described a procedure for needle biopsy of the kidney.[2] This was the first of many reports [3] which have contributed valuable information about diseases of this organ. There are, however, only a few studies which deal with the representative nature of the kidney-biopsy specimen.[4-6] The study being reported was done to explore the correlations which exist between diagnoses from needle biopsies of the kidney and those from routine autopsy specimens. Similar investigations were done when the value of needle biopsy of the liver was being established.[7-10]

Material and Methods

This study was begun in June, 1954. At that time no attempt was made at case selection. Needle biopsies of the kidney were done before and during almost every autopsy at the West Side Veterans Administration Hospital. After some experience had been gained in studying biopsy specimens from subjects without important histologic abnormalities of the kidney, the study was restricted, and biopsies were done only when the clinical records suggested the presence of renal disease. A total of 103 cases was studied (Table 1).

The first specimen was taken percutaneously prior to the autopsy. This was designated the "external specimen." With the body prone, a 12-gauge Turkel biopsy needle was inserted into the right kidney by use of the technique originally described by Iversen and Brun [2] and modified by Parrish.[11] External biopsies were done in only 38 cases, because kidney biopsy after death was found to be a more difficult procedure than during life. After the kidneys had been removed, a series of three or four biopsies were done with the same needle from the lower pole of the exposed right kidney; these were designated "direct specimens." This area was chosen because it was considered the one most commonly sampled by percutaneous needle biopsy. Finally, a routine autopsy specimen was taken from the same area. Each specimen was preserved in 10% formalin, embedded in paraffin, stained with hematoxylin and eosin, and examined by one of us (B. C.) without knowledge of other data pertaining to the case. The analysis included a description of Bowman's capsule, the glomeruli, the proximal convoluted tubules, Henle's loops, the distal convoluted tubules, the interstitial tissue, and the blood vessels. At the conclusion of this description a diagnostic interpretation was made.

A period of at least one month intervened between the reading of the external, the direct, and the autopsy specimens, respectively. These were identified by number only.

Results

Thirty persons without significant renal diseases were studied. The diagnoses for these patients are listed separately in Table 1. One hundred sixteen biopsy specimens were taken from the patients in this group. Only one specimen was misinterpreted and considered to be abnormal. An erroneous

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TABLE 1.—*Diagnoses in One Hundred Three Patients*

Major Diagnosis *	Renal Disease: Present Histologically	Renal Disease: No Histologic Evidence
1. Cardiovascular diseases	29	8
(a) Arteriosclerotic heart disease	2	
(1) With congestive heart failure	5	1
(2) With myocardial infarction	5	4
(b) Hypertensive cardiovascular disease	4	
(1) With congestive heart failure	1	
(2) With malignant hypertension	10	
(c) Rheumatic heart disease	2	3
2. Pulmonary diseases	3	12
(a) Bronchogenic carcinoma	2	6
(b) Metastatic pulmonary carcinoma		1
(c) Bronchiectasis		2
(d) Emphysema	1	2
(e) Chronic bronchial asthma		1
3. Gastrointestinal diseases	13	5
(a) Carcinoma of stomach	3	
(b) Carcinoma of gall bladder or bile ducts	1	1
(c) Carcinoma of duodenum		1
(d) Carcinoma of pancreas	5	
(e) Hepatoma	1	1
(f) Carcinoma of colon	2	
(g) Perforated peptic ulcer	1	
(h) Hemachromatosis		1
(i) Pseudomembranous colitis		1
4. Renal diseases	7	
(a) Glomerulonephritis		
(1) Subacute	1	
(2) Chronic	2	
(b) Pyelonephritis	2	
(c) Hypernephroma	1	
(d) Renal cortical necrosis	1	
5. Hematologic diseases	6	2
(a) Polycythemia	1	
(b) Acute leukemia	2	
(c) Hodgkins disease		1
(d) Lymphosarcoma		1
(e) Multiple myeloma	3	
6. Collagen diseases	4	1
(a) Lupus erythematosus	1	1
(b) Periarteritis nodosa	2	
(c) Wegener's granulomatosis	1	
7. Infections	4	
(a) Disseminated coccidioidomycosis	1	
(b) Disseminated histoplasmosis	1	
(c) Tuberculosis meningitis	1	
(d) Empyema & subdiaphragmatic abscess	1	
8. Diseases of central nervous system	1	2
(a) Cerebral thrombosis	1	
(b) Subarachnoid hemorrhage		1
(c) Cerebellar cyst		1
9. Genitourinary diseases	2	
(a) Carcinoma of urinary bladder	1	
(b) Rectovesicle fistula (suicide)	1	
10. Diabetes mellitus	2	
11. Kaposi sarcoma	1	
12. Fibrosarcoma	1	
Total patients	73	30

* Diagnosis based on clinical and autopsy records.

diagnosis of "acute glomerulitis with focal interstitial nephritis" was made in this instance on a section showing postmortem autolytic changes.

The biopsy results from patients with renal disease are shown in Tables 2 and 3. In Table 2 the histologic diagnoses are arranged according to the anatomic portion of the kidney primarily involved. If the histologic diagnosis included more than one renal disease, each has been listed separately.

TABLE 2.—*Histologic Diagnoses in Seventy-Three Patients with Renal Disease*

Diagnosis	No.	Total
Glomerular diseases		
Membranous glomerulonephritis	1	
Subacute glomerulonephritis	1	
Chronic glomerulonephritis	3	
Nephropathy accompanying lupus erythematosis	1	
Acute necrotizing glomerulonephritis	1	
		7
Tubular diseases		
"Cholemic nephrosis"[18]	2	
"Myeloma nephrosis"[14]	2	
"Osmotic nephrosis"[19]	2	
		6
Renal vascular diseases		
Benign arteriolar nephrosclerosis	24	
Malignant arteriolar nephrosclerosis	14	
		38
Renal diseases involving interstitial tissue		
Pyelonephritis		
Focal	13	
Diffuse	9	
		22
Nephrocalcinosis		
Focal	3	
Diffuse	1	
		4
Neoplastic diseases	4	
		4
Renal cortical necrosis	1	
		1
Total		82

TABLE 3.—*Correlation of Needle Biopsies with Autopsy Specimens*

Diagnosis	Pts., No.	Biopsies, No.			Biopsies with Histologic Changes Similar to Autopsy Specimens			Biopsy Diagnosis Same as Autopsy Diagnosis		
		Ext.	Dir.	Total	Ext.	Dir.	Total	Ext.	Dir.	Total
Glomerular diseases										
Membranous glomerulonephritis	1	1	4	5	1	4	5	0	4	4
Subacute glomerulonephritis	1	1	3	4	1	3	4	1	3	4
Chronic glomerulonephritis	3	1	10	11	1	10	11	0	6	6
Nephropathy accompanying lupus erythematosis	1	0	3	3	0	2	2	0	0	0
Acute necrotizing glomerulonephritis	1	0	1	1	0	1	1	0	1	1
Total	7	3	21	24	3	20	23 (96%)	1	14	15 (63%)
Tubular diseases										
"Cholemic nephrosis"[13]	2	0	8	8	0	7	7	0	7	7
"Myeloma nephrosis"[14]	2	1	8	9	1	6	7	1	6	7
"Osmotic nephrosis"[15]	2	0	7	7	0	7	7	0	3	3
Total	6	1	23	24	1	20	21 (88%)	1	16	17 (71%)
Renal vascular diseases										
Benign arteriolar nephrosclerosis	24	15	78	93	13	59	72 (77%)	13	59	72 (77%)
Malignant arteriolar nephrosclerosis	14	5	46	51	4	40	44 (86%)	4	40	44 (86%)
Total	38	20	124	144	17	99	116 (81%)	17	99	116 (81%)
Renal diseases involving interstitial tissue										
Pyelonephritis										
Focal	13	7	41	48	3	18	21 (44%)	2	13	15 (31%)
Diffuse	9	3	29	32	3	26	29 (91%)	3	21	24 (75%)
Total	22	10	70	80	6	44	50 (63%)	5	34	39 (49%)
Nephrocalcinosis										
Focal	3	1	12	13	1	4	5	1	4	5
Diffuse	1	1	4	5	1	3	4	1	3	4
Total	4	2	16	18	2	7	9 (50%)	2	7	9 (50%)
Neoplastic diseases	4	2	12	14	1	11	12 (86%)	1	11	12 (86%)
Renal cortical necrosis	1	0	4	4	0	4	4 (100%)	0	4	4 (100%)
Totals	82	38	270	308	30	205	235 (76%)	27	185	212 (69%)

A total of 82 diseases was found in the 73 patients who had histologic abnormalities.

Among seven patients with glomerular diseases (Table 3), five had some stage of glomerulonephritis, one had glomerular abnormalities consistent with lupus erythematosus, and the remaining patient (reported elsewhere[12]) had Wegener's granulomatosis with severe necrotizing glomerulonephritis. Twenty-four biopsies were done on these patients. In 15 of these specimens the histologic changes observed and the diagnoses made were the same as those on the autopsy specimens. In eight others the histologic changes were similar to the autopsy specimens, but the diagnostic conclusions were somewhat different. The postmortem specimen from the first patient showed chronic glomerulonephritis with superimposed pyelonephritis and diffuse nephrocalcinosis. Five biopsies were performed on this man's right kidney. Four were diagnosed membranous glomerulonephritis, and one was called nephropathy accompanying lupus erythematosus. At the time of each reading, however, the pathologist considered both of these conditions and indicated some doubt about his final conclusion. Several months later these slides were reviewed without reference to the previous readings, and again the pathologist considered both diseases but drew the same conclusions he had previously made. The second patient had lupus erythematosus. Three biopsies

were performed; two were called membranous glomerulonephritis, and one was considered abnormal, but no diagnosis could be made. The postmortem specimen from a third patient revealed focal membranous glomerulonephritis. One of five biopsy specimens was incorrectly considered normal.

Six patients were found to have tubular disease. As shown in Table 3, a histologic diagnosis of "cholemic nephrosis" [13] was made in two of these patients. Two others had "myeloma nephrosis," [14] and two had changes compatible with "osmotic nephrosis." [15] In 17 of 24 biopsies from these patients the diagnoses were identical with those on the postmortem section. In four others, all taken from a patient with "osmotic nephrosis," the significant changes were mentioned in the description, but the pathologist considered these within the limits of normal when making his final diagnosis. Two other biopsy specimens from a patient with "myeloma nephrosis" and one from a man with "cholemic nephrosis" failed to demonstrate the histologic changes.

There were 38 patients with arterial disease of the kidney. Twenty-four had benign arteriolar nephrosclerosis, and the other fourteen had malignant nephrosclerosis. Ten patients were recognized before death to be in the malignant phase of hypertension. Four others had a clinical diagnosis of hypertensive cardiovascular disease, although evidence of malignant nephrosclerosis was not demonstrated until the postmortem renal specimens were studied histologically (Table 1). As shown in Table 3, there was correlation with the autopsy diagnosis in 77% of 93 biopsies from persons with benign nephrosclerosis. Twenty-one biopsies did not reveal evidence of arterial disease. Fifty-one needle biopsy specimens were taken from the fourteen patients with malignant arteriolar nephrosclerosis. Forty-four (86%) of these specimens were interpreted correctly, and all of the remaining ones showed vascular changes which were called benign nephrosclerosis.

Twenty-two patients had evidence of pyelonephritis in the autopsy sections. Thirteen had focal pyelonephritis, while the remaining nine had diffuse involvement (Table 3). Forty-eight biopsies were performed on the patients with focal pyelonephritis, and fifteen (31%) showed diagnostic changes. On the other hand, 24 (75%) of 32 biopsies from the cases of diffuse pyelonephritis revealed diagnostic abnormalities. Some of the changes of pyelonephritis were observed in 50 of the 80 needle specimens studied. Twenty-seven of the negative specimens were from patients with focal pyelonephritis. Two of the remaining ones were from a patient with malignant nephrosclerosis, and all of the changes found were attributed to this disease. The final specimen was from a patient with benign nephrosclerosis, and again all of the abnormalities were considered to be secondary to vascular changes. Although 50 biopsy specimens contained some of the changes of pyelonephritis, the diagnosis was made on only 39 specimens. Four of the eleven biopsy specimens in which changes were described but no diagnosis made were from a patient with malignant nephrosclerosis and focal pyelonephritis. Five others were from the patient with chronic glomerulonephritis and superimposed diffuse nephrocalcinosis and chronic pyelonephritis, who was previously described in the group of glomerular diseases. All changes were attributed to the coexisting diseases. The remaining two needle specimens were from two patients, each of whom had focal pyelonephritis.

Evidence of nephrocalcinosis [16] was present in the autopsy sections of four patients. The diagnosis of 9 of 18 biopsy specimens from these patients corresponded with the autopsy diagnosis. One of the patients had diffuse nephrocalcinosis demonstrated on x-ray and confirmed in four of the five needle specimens obtained. This is the patient who also had chronic glomerulonephritis with superimposed pyelonephritis. The other three patients had a focal type of nephrocalcinosis. All five biopsy specimens

from a patient with multiple myeloma revealed these changes, but no calcium was found in four specimens from a patient with carcinoma of the stomach or in four other specimens from a patient with bronchogenic carcinoma.

Four patients had renal involvement by neoplastic disease. Twelve of fourteen needle specimens were positive in these four patients, who had the following diseases: myelogenous leukemia, bronchogenic carcinoma, hypernephroma, and carcinoma of the pancreas. Since this frequency of demonstrable involvement is unusually high in focal renal disease, it is important to note that only two patients had biopsies done before the body was opened. One specimen was normal, and the other revealed evidence of malignant involvement. The positive specimen was from the patient with leukemia.

One patient had bilateral renal cortical necrosis.[17] He was 49 years old and a chronic alcoholic and had evidence of cirrhosis and acute renal failure with anuria. He lived only 48 hours after admission, and at autopsy no definite cause for the necrosis of the renal cortex could be established. Four biopsies were performed, and all specimens showed evidence of the disease.

Comment

A study of the adequacy of needle-biopsy specimens from the kidney involves several considerations. The first, which this study was originally intended to explore, concerns the representative nature of the specimen. There has been some tendency to relate this to the number of glomeruli available for study. The presence of a large number of glomeruli is reassuring to the examiner and is particularly helpful in evaluating the severity of a disease. There are instances, however, when a satisfactory diagnostic conclusion cannot be reached even though many glomeruli are present. On the other hand, typical changes in only one or two glomeruli may occasionally suggest a specific diagnosis

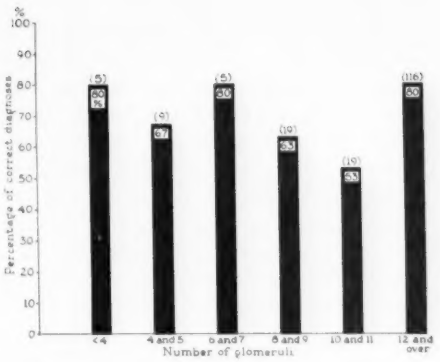

Fig. 1.—Comparison of the frequency of correct diagnosis with the number of glomeruli in a renal biopsy specimen. Figure in parenthesis represents the number of biopsy specimens in that group.

In Figure 1, the incidence of correct diagnosis in this study is related to the number of glomeruli in a specimen. This bar graph does not show greater accuracy of diagnostic interpretation as the number of glomeruli increase. It would appear that a specimen with at least four glomeruli is usually adequate for histologic study.

Another problem pertaining to the adequacy of the specimen concerns the ability of the examiner to arrive at the correct diagnosis from a study of the histologic features. This involves interpreting the abnormalities and relating them to specific diseases. This cannot always be done with assurance, and the pathologist may sometimes be unwilling to draw conclusions which would provide a specific diagnosis. The hardship of interpreting changes in small specimens adds to the difficulty. The pathologist is also handicapped by a classification of renal diseases which does not always blend with traditional clinical concepts. An example of these difficulties exists in the well-known difference between the use of the term "nephrosis" by the pathologist to refer to degenerative renal changes in the tubules and the clinical application of this term to a syndrome which results from glomerular diseases of many types. Similarly, clinical and pathological concepts appear to differ with respect to the group of

tubular diseases reported in this study. All of the diagnoses in this group are descriptive pathological terms which do not have important implications for the clinician. Actually, conditions associated with acute tubular necrosis are the only entities which the clinician recognizes as diseases primarily affecting the tubules. This study does not include any of these conditions. The abnormalities reported, however, are considered sufficient to establish the adequacy of the needle specimens for demonstrating tubular changes.

The same histologic changes as those found in the autopsy specimen were observed in 23 of 24 biopsy specimens from patients with glomerular diseases, in 21 of 24 from cases of tubular disease, and in 50 of 80 from those with pyelonephritis. Yet a biopsy diagnosis which corresponded exactly with the one from the postmortem specimen was made in only 15 of the 23 abnormal biopsy specimens from the glomerular disease group, in 17 of the 21 from tubular diseases, and in 39 of the 50 from pyelonephritis. Distinguishing certain stages of glomerulonephritis, particularly membranous glomerulonephritis, from the nephropathy accompanying lupus erythematosus is a difficulty which many have encountered.[18] Inability to make this distinction consistently was responsible for the discrepancies in the group of glomerular diseases. Discrepancies in the other groups were analyzed in previous portions of this paper. In some instances, the disease was a focal one and significant changes were not found in the needle sections. In others, all changes were attributed incorrectly to coexisting diseases or were felt to be within the variations of normal.

Considering the complexity of the problem of needle biopsy of the kidney, it has been reassuring that only 1 of 116 biopsy specimens from 30 patients with no histologic evidence of renal disease was misinterpreted. The correct diagnosis was made in 69% of the total biopsies in this study. Changes similar to those in the autopsy specimen were demonstrated in an additional 7% of the needle specimens (Table 3). It is to be emphasized that 27 of 38 external biopsies (71%) were positive. This percentage is almost exactly the same as the total for correct diagnoses in the entire study (69%). This would suggest

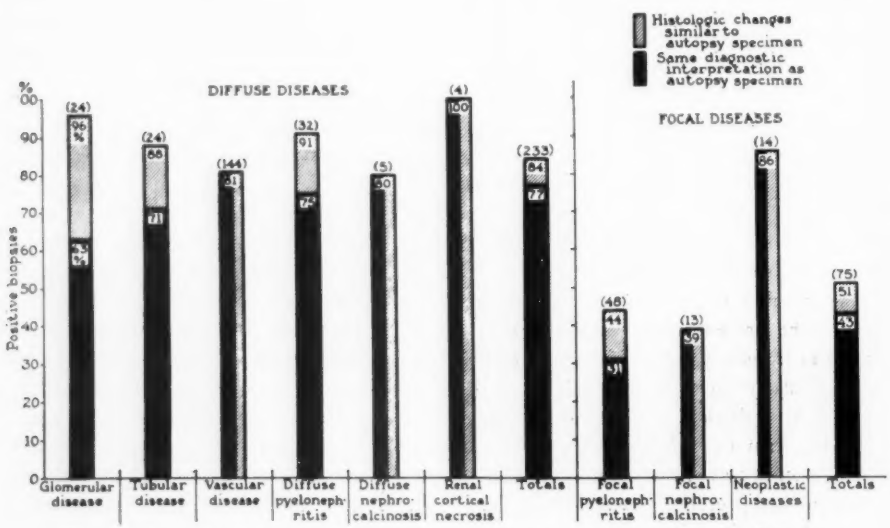

Fig. 2.—Comparison of needle biopsy results in diffuse and focal renal diseases. Figure in parenthesis represents total biopsy specimens in that group.

that there was no bias in selection of the biopsy site when specimens were taken directly from the exposed kidney. The results of needle biopsies from patients with diffuse renal diseases are contrasted with those from patients with focal diseases, in Figure 2. There is remarkable consistency in the various subgroups of diffuse renal diseases, and an average of 84% of all these biopsy specimens were positive. This is in contrast to the focal disease category, in which only 51% of the total biopsy specimens were positive.

Summary

Needle biopsy specimens of the kidney were obtained post mortem in 103 cases. The representative nature of the biopsy specimen was evaluated by comparison of the histologic features and diagnostic conclusions from multiple biopsies with the final autopsy diagnosis. Seventy-six per cent of 308 biopsy specimens accurately reflected the primary histologic abnormality, and in sixty-nine per cent the correct diagnosis was made. In general, this procedure is more likely to provide information concerning a specific diagnosis when a diffuse renal disease exists than when the disease is focal.

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Chlorpropamide in the Management of Diabetes

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Chlorpropamide is a new oral antidiabetic agent. Its chemical name is *N*-propyl-*N'*-(*p*-chloro-benzenesulfonyl)urea. The structural formula (Fig. 1) is similar to other sulfonamide derivatives which have been observed to have a blood-sugar-lowering effect.

Schneider et al.,[1] in a thorough pharmacological study of more than two years' duration, found chlorpropamide to be an effective, orally active hypoglycemic agent. In the rhesus monkey, this compound was found to be considerably more potent than tolbutamide and, in addition, the duration of the hypoglycemic effect was more prolonged.

The purpose of the investigation reported here was to confirm the antidiabetic properties of chlorpropamide in the human, to study its therapeutic effectiveness, and to disclose the presence or absence of significant side-effects. In particular we wished to observe the effectiveness of chlorpropamide in those patients who were unresponsive to tolbutamide.

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The chlorpropamide used in this study was supplied as Diabinese, by Dr. D. G. Iezzoni, of Chas. Pfizer & Company, Inc., Brooklyn.

From the Medical Department of Prince Georges General Hospital, Cheverly, Md., and the Diabetic Clinic, George Washington University Division, District of Columbia General Hospital, Washington, D. C. Associates in Medicine, George Washington University School of Medicine (Drs. Sugar and Thomas), and Resident in Medicine, Prince Georges General Hospital (Dr. Eugenio).

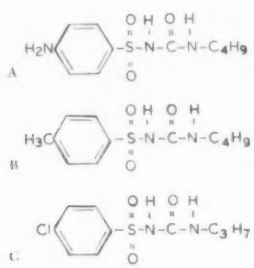

Fig. 1.—Structural formulae of hypoglycemic sulfonamide derivatives: *A*, carbutamide; *B*, tolbutamide (Orinase); *C*, chlorpropamide (Diabinese).

Method of Study

Diabetic patients who were taking insulin, those inadequately controlled with tolbutamide, and an occasional patient only partly controlled by diet alone were studied. The first few patients were hospitalized, but as we became more familiar with the drug it was given to clinic and ambulatory private patients. Diet was prescribed according to optimal caloric requirements. A daily dose of chlorpropamide was administered as described below.

In the hospital, fractional urinalyses for sugar and acetone were made by the ward nurses before meals and at bed time. Each test showing more than a trace of sugar (Clinitest * modification of Benedict's test) was covered by an injection of regular insulin, ranging in dosage from 5 to 20 units, depending on the percentage of sugar present. In this way we were able to prevent ketosis and at the same time observe the degree of effectiveness of chlorpropamide. Daily fasting blood sugar, an occasional blood sugar after a meal, and 24-hour quantitative urine glucose determinations were made as added parameters of control.[2]

Management with chlorpropamide was considered satisfactory if the average daily fasting blood sugar was substantially reduced and was in the region of 200 mg. per 100 ml. or below. Urine tests were required to be negative or show less than 0.25% sugar. When at least three days' observation indicated these requirements had been attained, patients were given a supply of medication and discharged, to be followed in the outpatient clinic. Particular stress was made on the need for frequent urine tests at home, and a written record of the results was requested. On returning to the clinic, the patient was examined, home urine tests reviewed, and

* The Clinitest apparatus and tablets are manufactured by The Ames Co., Inc., Elkhart, Ind.

the fasting blood and urine sugar for that day determined. If most of the urine tests were reported negative for sugar and if the blood sugar was below 120 mg. per 100 ml., the dose of chlorpropamide was reduced by half. If the blood sugar was between 120 and 175, the dose was maintained. If it was above 175 and the urine tests showed considerable amounts of glucose, the dose was increased by 0.25 gm. increments until the blood and urine sugar levels showed better control.

In a similar manner, the patients not hospitalized were given the drug and requested to test the urine at home at least twice daily. Those taking insulin were given chlorpropamide concomitantly. Usually the dose of insulin was lowered by decrements of 10 units, as control was maintained by a constant dosage of chlorpropamide until eventually no insulin was needed. If the blood and urine tests showed increasing amounts of glucose, chlorpropamide was stopped and insulin dosage adjusted until control again was apparent. Patients were seen at weekly intervals until management was considered satisfactory; thereafter the frequency of visits was decreased as improvement progressed.

Those patients taking tolbutamide but having persistent glycosuria and fasting blood sugar levels always above 200 mg. per 100 ml. were considered not adequately managed. They were placed directly on chlorpropamide and followed in the same manner as above.

Chlorpropamide was made available initially in uncoated tablets containing 0.5 gm. In a previous report,[3] we noted satisfactory management of several patients with as little as 0.25 gm. a day. In order to provide flexibility of dosage, chlorpropamide is available now (as Diabinese) in 100 mg. and 250 mg. scored tablets.

The first few patients treated by us were given an initial priming dose of 2.5 gm. As our studies continued it was found that a starting dose of 1.0 gm. per day in two doses, given before breakfast and supper, proved most effective. However a number of side-effects, described below, were thought to be related to this dosage. Finally, a dose of 0.5 gm. per day was selected as starting therapy. Comparatively few symptoms of toxicity appeared with this amount of drug.

After one week, if control was not satisfactory, the dose was increased by increments of 0.25 gm. No patients benefited by an increase in the dose to more than 1.5 gm. When good control was manifested by a lowering of fasting blood sugar and negative urine sugar tests, the dose was decreased, usually by decrements of 0.25 to 0.125 gm.

Results

A total of 84 patients were treated with chlorpropamide from 2 to 11 months. Fifty-two of these (62%) were satisfactorily managed. Cases were subdivided into usual diabetics who were controlled with insulin or only partly controlled with diet alone and those who had received tolbutamide but were not in control. The latter group was further subdivided into "primary tolbutamide failures," that is, patients who failed to respond to tolbutamide within the first month of treatment, and "secondary tolbutamide failures," or those patients who had slipped out of control after a variable period of satisfactory management with tolbutamide. The results of treatment in each group are outlined in Table 1.

TABLE 1.—*Results of Treatment*

	No.	%
Patients previously treated with insulin or partly controlled with diet	37	
Satisfactory control with chlorpropamide	27	73
Patients primarily unresponsive to tolbutamide	10	
Satisfactory control with chlorpropamide	2	20
Patients primarily responsive to tolbutamide but later losing control	37	
Satisfactory control with chlorpropamide	23	62
Over-all total of patients treated	84	
Satisfactory control with chlorpropamide	52	62

Twenty-seven out of thirty-seven (73%) usual diabetics were adequately managed with chlorpropamide alone. Only 2 of 10 "primary tolbutamide failures" responded to chlorpropamide. However, 23 out of 37

TABLE 2.—*Analysis of Patients Treated with Chlorpropamide*

Age, Yr.	Patients Treated, No.	Successful No.	Successful %
20-39	8	3	37.5
40-59	41	27	67.3
60-80	35	27	77
Duration of Diabetes, Yr.			
0-9	62	40	64.5
10-19	14	9	64
20-31	8	3	37.5
Insulin Dosage, Units			
0-19	12	12	100
20-39	16	10	62
40-59	8	5	62
60-80	1	0	0

(62%) "secondary tolbutamide failures" responded to chlorpropamide. Six of fourteen patients in this group responded to a second course of tolbutamide when chlorpropamide had to be discontinued.

Best results were noted in patients over the age of 40 whose known existence of diabetes was less than 10 years and who were taking less than 40 units of insulin (Table 2). The course of a typical successful result is shown in Figure 2. As our studies progressed, several patients showed a gradual decrease in blood sugar over several months of administration of chlorpropamide even though the dose of drug was gradually reduced (Fig. 3). In fact, an occasional patient remained well controlled as long as eight months after chlorpropamide was discontinued altogether (Fig. 4). Similar results were reported by one of us for tolbutamide.[4] It would seem that in some patients chlorpropamide has a cumulative effect.

Toxicity

Side-reactions to chlorpropamide are listed in Table 3. In retrospect we believe many of these symptoms could have been avoided by starting with a small dose, of 0.25 to 0.5 gm., per day. Abdominal discomfort frequently associated with anorexia and nausea was most prominent with doses of

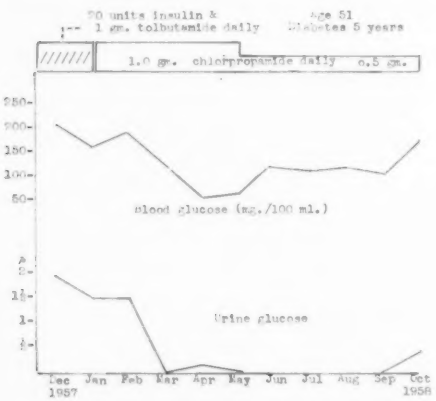

Fig. 2.—Good control with chlorpropamide in a patient previously managed with insulin and tolbutamide.

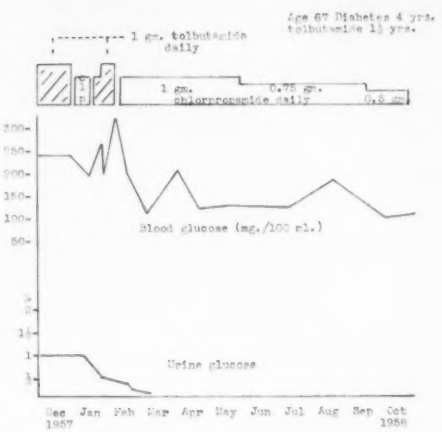

Fig. 3.—Good response to chlorpropamide in a "secondary" tolbutamide failure.

1.0 gm. or more per day. Substernal and epigastric pain, severe enough to warrant cardiovascular investigation, was noted in eight patients. Electrocardiograms in all of these showed evidence of coronary artery disease. Two cases in this group later developed characteristic signs and symptoms of myocardial infarction. Chlorpropamide was continued in two patients, and the chest pain gradually subsided. In fact two cases were given the drug, with good effect,

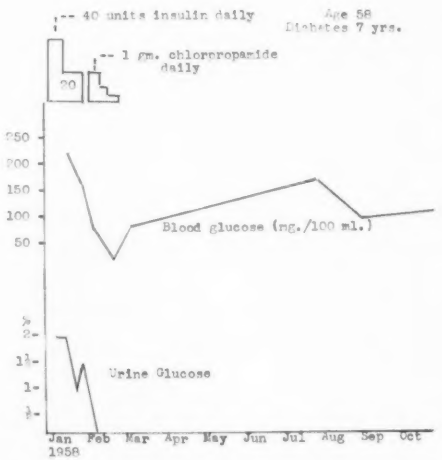

Fig. 4.—Good control continuing after stopping chlorpropamide.

TABLE 3.—*Side-Reactions to Chlorpropamide*

	Patients, No. *
Abdominal discomfort, anorexia, nausea, vomiting	9
Substernal pain	8
Muscle weakness	7
Hypoglycemic symptoms (anxiety, hunger, sweating)	4
Rash & itching	4
Peculiar taste, numbness of tongue	3
Leukopenia (2,500)	1

* Total number of patients treated, 84.
2 or more of the above reactions were noted in several patients.

soon after suffering an acute coronary artery occlusion.

Complaints of weakness, usually in the muscles of legs, arms, and abdomen, were severe enough to warrant stopping medication in two patients. There was no alteration in serum potassium levels in these cases. Blood sugar values were not markedly reduced, and the symptoms were not relieved by glucose administration. A direct effect on muscle function by chlorpropamide must be considered.

Typical hypoglycemic symptoms of anxiety, hunger, and sweating associated with low blood sugar values were noted in four patients. These complaints disappeared promptly with administration of sweet drinks and did not recur when dose was reduced. There were no cases of coma.

Four patients with itching and two with associated maculopapular rash of face, arms, and legs were noted. One of these was severe enough to warrant discontinuation of the drug, but the others responded to antihistamine preparations while continuing treatment with chlorpropamide.

Three patients had an excellent response to a daily dose of 1.0 gm. but asked for a change of medication because of a disagreeable taste sensation. This was described as a "sick, sweet taste even in the lips." Again, we believe this could have been avoided by starting with a smaller daily dose, of 0.5 gm.

One case of leukopenia with a white blood cell count of 2,500 was noted. There was no specific depression of polymorphonuclear cells of lymphocytes, and when chlorpropamide was discontinued the count promptly returned to normal. This patient was a "brittle" diabetic and had been given a daily dose of 2.0 gm. of chlorpropamide for two weeks in an effort to control the disease.

A depression of thyroid uptake of radioiodine was noted in six patients. The range of lowering was 4% to 15%. There were no associated symptoms of hypothyroidism, and this reaction was considered of no clinical significance.

No unusual effects on kidney or liver have been noted by us. Several patients have been observed for as long as 11 months while taking a daily dose of chlorpropamide.

One patient died of coronary thrombosis after having been controlled with chlorpropamide for four months. He was known to have malignant hypertension, and his death was in no way attributable to the drug.

Conclusions

Of 84 diabetics studied, 62% were satisfactorily controlled with chlorpropamide.

The most easily controlled were middle-aged patients with relatively recent onset of diabetes requiring less than 40 units of insulin per day.

Of patients who lost responsiveness to tolbutamide, 62% were satisfactorily managed with chlorpropamide.

Toxicity to chlorpropamide is somewhat related to dosage. Gastrointestinal symptoms, chest pain, and muscular weakness were the most prominent side-effects. Occasionally these were relieved by reduction in dose of the drug.

Chlorpropamide is more potent than tolbutamide in blood-sugar-lowering ability.

Unstable diabetics of any age are poor candidates for control with chlorpropamide.

Most patients responded to a daily dose of 0.25 to 0.5 gm. Doses of more than 1.0 gm. a day are frequently associated with unpleasant side-effects.

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Antibiotic Susceptibility and Phage Types of Pathogenic Staphylococci

A Study of Two Hundred Ten Strains Isolated at Boston City Hospital in 1955

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The antibiotic susceptibility of pathogenic staphylococci obtained from patients at the Boston City Hospital has been reported on several occasions in the past, and the results of studies carried out on such organisms isolated and studied prior to 1954 have been reviewed elsewhere.[1,2] The present paper deals with coagulase-positive staphylococci isolated at this hospital in the latter half of 1955 and their susceptibility to some antibiotics that had been used extensively and to others that had not been available prior to the isolation of these strains. The susceptibility of the isolates to the most extensively used antibiotics has been correlated with their bacteriophage types and with prior antibiotic treatment of the patients from whom they were obtained.

Materials and Methods

Strains.—A total of 210 cultures of Staphylococcus pyogenes var. aureus, nearly all of them isolated between Aug. 28 and Nov. 3, 1955, were included; the majority were obtained before therapy with antibiotics was started at this hospital or at the time when changes in the antibiotic therapy were made; about one-fifth were isolated at autopsy. Of the cultures made during life, 45% were from soft-tissue abscesses or infected wounds; 21%, from blood; 18%, from exudates of body cavities (pleural, peritoneal, synovial, aural, or cerebrospinal fluids); 12%, from the respiratory tract (nasopharyngeal swabs, sputum, or tracheobronchial aspirates), and 2% each, from urine and feces; the majority of those obtained at autopsy were from the lungs or from cardiac blood, but one-fourth of them came from purulent foci in sites other than the lung. Each "strain" represents growth from a single colony isolated from the culture and maintained by subsequent subcultures on agar.

Antibiotics.—The following antibiotics were used in the sensitivity tests: penicillin G, streptomycin, tetracycline, chloramphenicol, erythromycin, bacitracin, neomycin, novobiocin, synnematin B* (Abbott Laboratories), oleandomycin (Chas. Pfizer & Company), spiramycin (Merck & Co., Inc.), paromomycin (Parke, Davis & Company), kanamycin (Bristol Laboratories), streptogramin (Antibiotic 900, Merck & Co., Inc.), vancomycin (Eli Lilly and Company), ristocetin (Abbott Laboratories), Bryamycin (Bristol Laboratories), and Antibiotic MK 111 (Merck & Co., Inc.). Only one-half of the strains were tested with the last five agents, but nearly all were tested with the others.

Tests for Sensitivity.—These were done by Clare Wilcox, Ann Najarian, and George Kacoyanis by use of the plate-dilution method employed in previous studies from this laboratory. A 2 mm. loopful of an overnight broth culture of the organisms was streaked on the surface of each of a series of plates of heart-infusion agar containing twofold dilutions of the antibiotic. The results were expressed as the minimum inhibiting concentration of the antibiotic on which there was no visible growth after incubation at 37 C for 24 hours.

Bacteriophage Typing.—This was carried out in the Biological Division of the Department of Medicine, The Johns Hopkins University, by Mary C. Rose. The methods employed for typing, including propagation and titration of the 25 standard bacteriophages used, have been described in detail by Blair and Carr.[3] The results of typing in this series were selectively checked by Dr. John E. Blair.

In the accompanying tables, the results of typing with concentrated phages and also weak reactions to standard dilutions of phage have been recorded in italics. At present, the significance of

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* Also known as cephalosporin N.

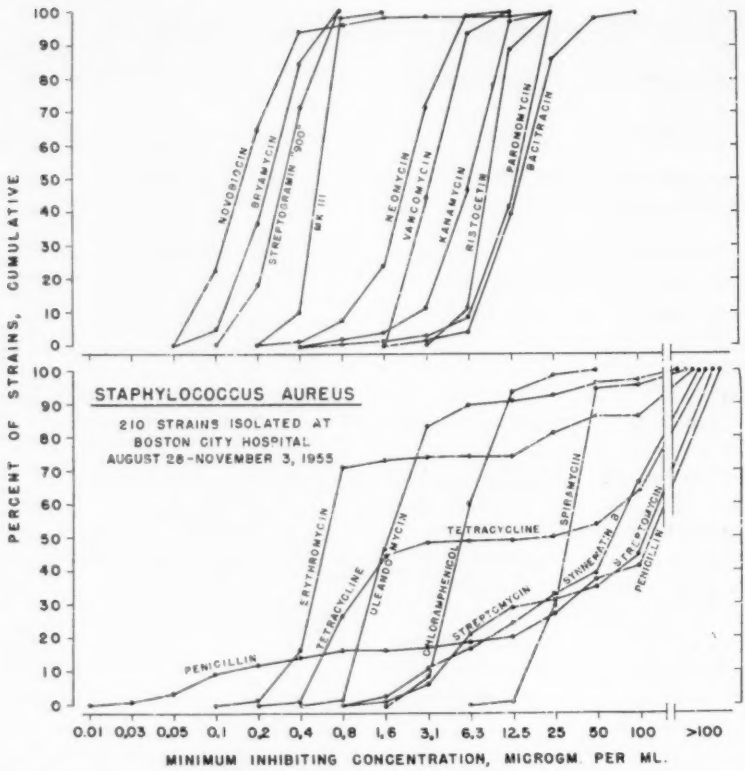

Fig. 1.—Susceptibility of 210 strains of S. pyogenes var. aureus to 18 antibiotics. The antibiotics represented in the upper panel were not available or had rarely been used prior to the isolation of these strains; those in the lower panel had been used frequently or are closely related drugs.

such reactions is not known,[4] and they are included here only for the sake of completeness.

Results

Susceptibility of Strains to Eighteen Antibiotics.—A summary of the results of all the tests for susceptibility to each of the 18 antibiotics is presented in Figure 1. For each antibiotic the susceptibility of all the strains tested is shown as the cumulative percentage inhibited by increasing drug concentrations. The upper panel of this figure depicts the results obtained with 10 antibiotics which had never been used for therapy at this hospital before these strains were isolated. Exceptions were neomycin and bacitracin, which had been used together for topical application in a few cases; the latter agent had occasionally been given intramuscularly to supplement other antistaphylococcal antibiotics. None of these 10 antibiotics have shown cross resistance with any of the more commonly used antibiotics, except streptogramin, which shows some one-way cross resistance in vitro to antibiotics of the erythromycin group.[5] Kanamycin and paromomycin have spectra of antibacterial activity identical with that of neomycin, and cross resistance among these three is almost complete in strains made resistant in vitro or in those freshly isloated from patients.[6]

The curve for each of these 10 antibiotics shows the S-shape of a "normal" distribu-

tion pattern. Moreover, the relatively narrow spread between the minimal and maximal inhibitory concentrations of the most susceptible and the most resistant of the strains of each of these 10 antibiotics for these strains reflects the uniformity of their susceptibility to these agents. A minor exception is novobiocin, with which one strain was inhibited by 12.5μg. and another by 25 μg. per milliliter, whereas the remaining 208 strains were inhibited by concentrations ranging from 0.1μg. to 1.6μg. per milliliter.

The lower panel of Figure 1 summarizes the results with the other eight antibiotics. Five of these—penicillin, streptomycin, tetracycline, chloramphenicol, and erythromycin—had been used extensively in this hospital; the other three had never been used but are related to one or another of these five agents in chemical structure or biologic activity. Synnematin B is closely related to penicillin G,[7,8] and oleandomycin and spiramycin have spectra of antibacterial action similar to that of erythromycin, and cross resistance to organisms made resistant to any one of them in vitro is complete.[5]

Each curve, except the one for chloramphenicol, shows a wide spread between minimal and maximal inhibitory concentrations for these staphylococci. Moreover, there is a consistent flattening of the midportion of each curve; this is especially striking for penicillin, streptomycin, tetracycline, and erythromycin. Sixteen per cent of the strains were highly susceptible and were inhibited by concentrations of 0.8μg. of penicillin per milliliter, but only four per cent more were inhibited by concentrations up to 25μg. per milliliter; the remaining eighty per cent required greater concentrations or were not inhibited by 100μg. per milliliter. Streptomycin inhibited 29% of the strains in concentrations up to 12.5μg. per milliliter, and 56% were not inhibited by 100μg. per milliliter; only 14% of the strains fell into the intermediate zone. The tetracycline curve shows that 48% of the strains were inhibited by concentrations ranging from 0.8μg. to 3.1μg. per milliliter and an additional 2% by 6.3-25μg. per milliliter; the rest required 50μg. or more per milliliter. Erythromycin inhibited 70% of the staphylococci in concentrations up to 0.8μg. per milliliter, and an additional 4% required concentrations in the range of 1.6μg. to 12.5μg. per milliliter; the remaining 26% were more resistant.

The curves for oleandomycin and erythromycin are similar, except that a smaller proportion of the strains were resistant to the former. The steep rise of the curve for oleandomycin lies well to the right of that for erythromycin, indicating that strains susceptible to both of these agents required four or more times as much oleandomycin as erythromycin to inhibit them. The strains that were resistant to oleandomycin were all resistant to erythromycin as well, but some of the erythromycin-resistant strains were susceptible to oleandomycin.

The curve for spiramycin shows that this antibiotic was not highly active, but most of the strains were uniform in their

TABLE 1.—*Correlation Between Susceptibility to Penicillin and Synnematin B in 192 Strains of S. Pyogenes Var. Aureus Isolated at Boston City Hospital in 1955*

Penicillin G, μg/Ml.	Synnematin B, μg/Ml.								
	1.6	3.1	6.3	12.5	25	50	100	>100	Total
	Strains, No.								
<0.1	4	11	7	0	0	0	0	0	22
0.2-0.8	0	5	7	0	0	0	0	0	12
1.6-12.5	0	0	2	3	2	2	0	0	9
25-100	0	0	0	5	11	3	2	4	25
>100	0	0	0	0	2	6	49	67	124
Total	4	16	16	8	15	11	51	71	192

susceptibility, 96% being inhibited by 25μg. or 50μg. per milliliter, and only 1% of strains were more sensitive. The 3% of the strains that were not inhibited by spiramycin at 100μg. per milliliter were all resistant to erythromycin as well.

The results with synnematin B generally resembled those with penicillin. The correlation between the susceptibility of individual strains to these two antibiotics was close but not perfect, as shown in Table 1. The staphylococci that were most susceptible to either agent were inhibited by much lower concentrations of penicillin than of synnematin B. Among the strains that were resistant to 100μg. of penicillin per milliliter, some were inhibited by 25μg.-100μg. of synnematin B per milliliter.

The curve for chloramphenicol is the only one in the lower panel of Figure 1 (excluding that of spiramycin, with which comparisons are difficult) that closely resembles the normal distribution curve. In this connection it is of interest that of the five antibiotics that had been used regularly at this hospital prior to this study, chloramphenicol is the one to which it was found most difficult to induce a high grade of resistance in staphylococci in vitro.[9] Moreover, among the patients from whom these strains were isolated, chloramphenicol had never been given as the only antibiotic; with one exception it had always been administered in combination with erythromycin.

Effect of Previous Antibiotic Therapy.—Sixty-two of the strains were obtained from patients who had received no antibiotics at this hospital, and, as far as could be ascertained from their records, they had not taken any antibiotics during the several months preceding their admission to the hospital. Three of these sixty-two came from patients who had previously received sulfonamide drugs. Almost all of these cultures were obtained at the time of admission or when infection was first suspected. The remaining 148 strains were isolated from patients who had already received antibiotic therapy; in 80% of these cases, multiple antibiotics had been given.

Except in two patients in whom streptomycin was the only antibiotic used (although it had been given together with isoniazid for the treatment of tuberculosis), this antibiotic, as well as chloramphenicol and erythromycin, has not been given alone to any patient; in fact, chloramphenicol and erythromycin had almost always been given together, and in most instances additional antibiotics had also been administered. The most frequently used combination was penicillin and streptomycin. Only 19 strains were isolated after the administration of a single antibiotic; 11, after penicillin; 2, after streptomycin, and 6, after tetracycline. In summary, the therapy employed prior to isolation of the 148 strains included penicillin for about one-third of the strains, streptomycin or tetracycline each for about one-fifth, and chloramphenicol and erythromycin for slightly more than one-eighth.

In view of these facts about the therapy of the patients prior to isolation of the strains, their susceptibility to the commonly used antibiotics was compared only on the basis of whether or not the patients from whom they were isolated had previously been given any antibiotic, and no attempt was made to correlate the results with the individual antibiotics that had been given. Also, because of the more or less uniform susceptibility of the strains to chloramphenicol, comparisons were made only for penicillin, streptomycin, tetracycline, and erythromycin. The results are depicted graphically in Figure 2.

In the correlation of the data from which this figure was constructed, the post-treatment strains isolated during life were at first considered separately from those obtained from cultures made at autopsy. For penicillin, streptomycin, and erythromycin the curves representing the post-treatment strains that were obtained during life and those isolated at autopsy were so similar that all of the post-treatment strains were considered together in construction of the figure. In the tests for susceptibility to tetracycline, however, the strains isolated at

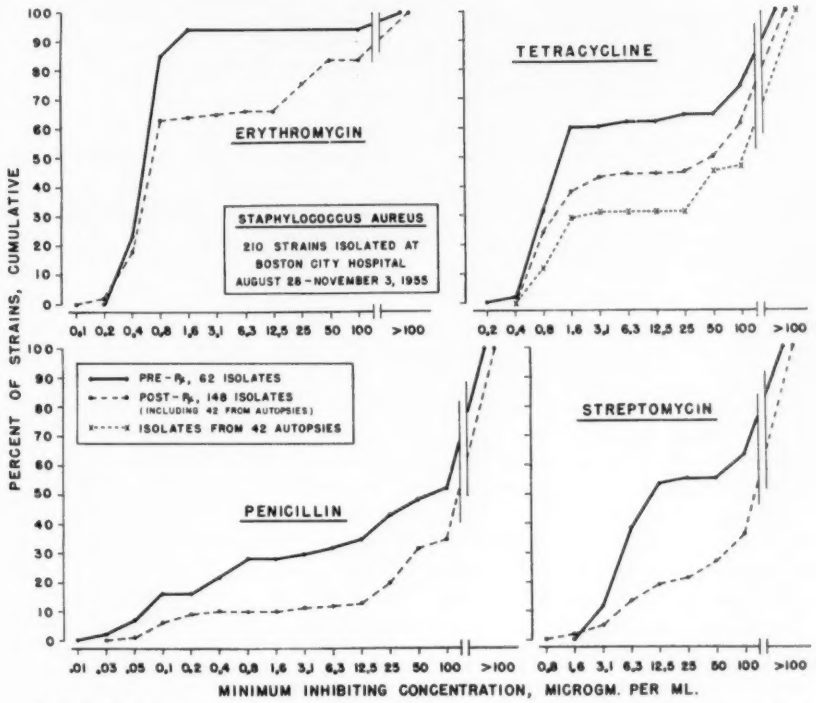

Fig. 2.—Relation of susceptibility of strains of S. pyogenes var. aureus to four widely used antibiotics to prior antibiotic treatment of the patients from whom they were isolated.

autopsy differed appreciably from the post-treatment strains isolated from living patients, and so the autopsy strains are depicted separately.

Figure 2 shows clearly that the pretreatment strains included a larger proportion of more susceptible staphylococci than did the post-treatment ones. In addition, it is evident that the autopsy cultures included a higher proportion of strains resistant to tetracycline than did those obtained during life. Previous studies [1] had also shown a higher proportion of penicillin-resistant strains of S. pyogenes var. aureus among those isolated from autopsies in 1950 than in any series that had been studied, except for a group of fecal strains isolated in 1951 during treatment with oxytetracycline.

In another study [10] of 500 strains of pathogenic staphylococci isolated at this hospital during 1951-1952, a close correlation between the incidence of strains resistant to certain antibiotics and their prior use in the treatment of the patients from whom the organisms had been isolated was not demonstrable. However, the findings in that study led to the suggestion that while previous treatment of individual patients may be a factor in the occurrence of resistant strains, the widespread use of antibiotics is of at least equal importance. Such strains may retain their resistance while they are disseminated and acquired by patients who have themselves not received such antibiotics. The data in the present study are consistent with this concept.

Phage Types and Patterns.—A total of 180 of the staphylococcal strains included in this study were subjected to phage typing. The results are summarized in Table 2. The commonest phage pattern was 52/42B/81; sixty-one strains reacted to

TABLE 2.—*Summary of Occurrence of Staphylococci of Different Phage Patterns and Their Relation to Previous Antibiotic Therapy*

Phages Lysed	Strains		Strains from Patients Not Previously Treated with Antibiotics	
	No.	%	No.	% of Phage Category
52/42B/81	61 *	34	20	33
Others	71 †	39	24	34
Nontypable	48	27	18	38
Total	180	100	62	34

* Includes 16 strains that also reacted with one additional phage (11 with 52A, 4 with 44A, and 1 with 42A).

† See Table 3.

these three phages. It is also noted that 16 of the same strains were lysed (weakly in most instances) by one additional phage; the significance of this finding is doubtful. Slightly more than one-fourth of the strains failed to react to any of the phages used, and 36 different phage types or patterns were represented among the remaining 71 strains (Table 3).

Relation of Phage Types to Previous Antibiotic Therapy.—In view of the findings noted in Figure 2, it was of interest to determine the distribution of phage types among these strains. From Table 2 it can be seen that the distribution of phage types among strains from untreated patients was very similar to that among the strains from treated persons.

Relation of Phage Types to Susceptibility of Staphylococci to Four Most Commonly Used Antibiotics.—The susceptibility of the staphylococci to penicillin, streptomycin, tetracycline, and erythromycin showed a distinct relation to their bacteriophage types. In Figure 3 it is seen that almost all staphylococci of the Phage Pattern 52/42B/81 were highly resistant to penicillin and to streptomycin and only about 16% of them were susceptible to tetracycline. The 71 other typable strains showed the highest proportion of strains sensitive to each of these three antibiotics, and the nontypable strains exhibited an intermediate distribution. However, the same relationships did not hold for susceptibility to erythromycin; nearly all of the 52/42B/81 strains were highly susceptible to erythromycin, only 8% being moderately or highly resistant to this antibiotic. The nontypable group had the greatest proportion of erythromycin resistance, and the distribution of erythromycin-sensitive and erythromycin-resistant strains among the other phage types was intermediate.

The reason for the differences in distribution of strains resistant to these four antibiotics can only be surmised from the history of antibiotic therapy at this hospital

TABLE 3.—*Occurrence of Phage Types and Patterns Among Seventy-One Strains of Staphylococci That Were Lysed by Phages Other Than 52/42B/81* *

Phage Types Lysed	Strains, No.	Phage Patterns Represented, No.	Individual Phage Types Represented, No.	Designation of Phages Represented
1 †	25	11	11	7, 39, 42D, 44A, 52, 53, 54, 70, 77, 79, VA4
2 ‡	30	11	14	3B, 3C, 6, 42B, 44A, 47, 52, 52A, 54, 73, 77, 79, 81, VA4
3 §	7	6	11	7, 44A, 47, 52, 52A, 53, 54, 73, 75, 79, VA4
4-6 ‖	9	8	14	6, 42B, 42D, 47, 52, 52A, 53, 54, 73, 75, 77, 79, 81, VA4
1-6	71	36	20	

* See Table 2 and footnotes.

† The largest number of strains lysed by any single phage was 5 (by Type 79); Types 44A and 54 each lysed 4 strains, and Types 7 and 52 each lysed 3 strains.

‡ The most frequent patterns were 52A/79 (10 strains), 52/52A (7 strains), and 52/42B (3 strains), and 2 strains each were lysed by 42B/81 and 47/VA4.

§ 2 strains lysed by 47/54/75.

‖ 2 strains lysed by 53/73/77/VA4.

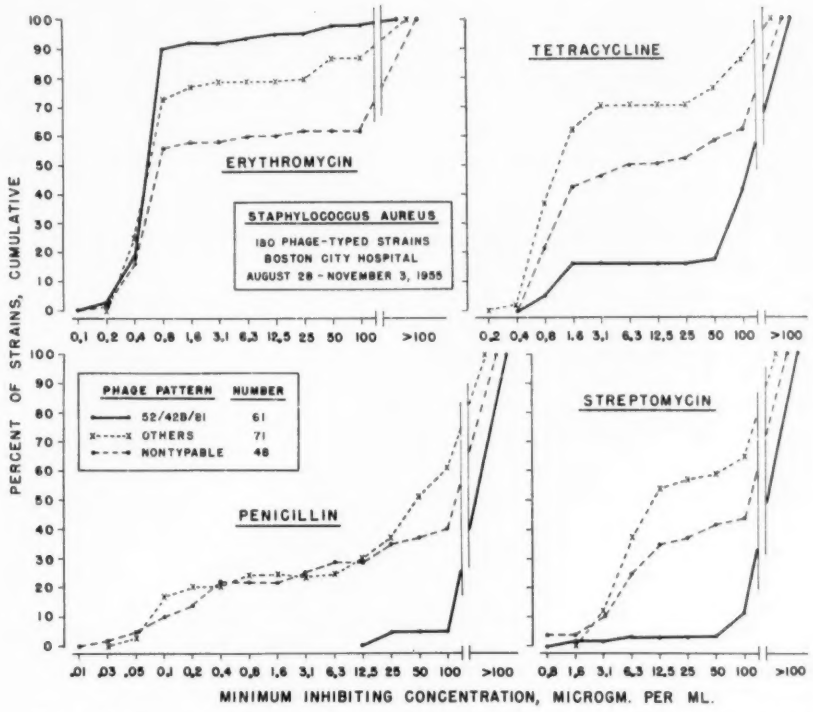

Fig. 3.—Relation of phage types of S. pyogenes var. aureus and susceptibility to four widely used antibiotics.

and in this community. The use of erythromycin had been under complete control at this hospital from the time this agent first became available until two years after all the strains for this study had been collected. Its use was almost entirely limited to the treatment of proved staphylococcal infections. Chloramphenicol was always given together with erythromycin for this purpose, and other antibiotics were often used in addition. If the 52/42B/81 infections are considered to be of hospital origin, the continued susceptibility of these strains to erythromycin during the period of this study may thus be explained. No such control over the use of erythromycin existed in the community at large, and many physicians have prescribed this antibiotic alone for all varieties of infections. This may account for the greater incidence of erythromycin-resistant strains among the other staphylococci, more of the infections with those organisms having originated outside the hospital. During the past year the use of erythromycin and chloramphenicol has been released from strict control of this hospital, and there already is evidence that a greater proportion of hospital-acquired staphylococcal infections are being caused by erythromycin-resistant strains. A further series of strains from staphylococcal infections is currently being assembled for a detailed study of these factors.

Phage Types and Antibiotic Susceptibility of Multiple Strains of S. Pyogenes Var. Aureus Isolated from Same Patients.—Table 4 lists the sources, phage patterns, and susceptibility to six antibiotics of staphylococci isolated at different times from 19 patients whose organisms exhibited changes either in phage type or in antibiotic susceptibility during treatment of an infection.

TABLE 4.—*Phage Types and Antibiotic Sensitivity of Multiple Isolates of S. Pyogenes Var. Aureus in Relation to Antibiotic Therapy*

Patient	Date (1955)	Source	Phage Pattern *	Previous Antibiotic Therapy †	Minimum Inhibiting Concentration, ug/Ml.					
					P †	S	T	C	E	O
1	Sept. 22	Throat	42B/52/81	T4	>100	>100	100	6.3	0.8	3.1
	Sept. 24	Blood	42B/52/81	T6	>100	>100	100	6.3	0.8	3.1
	Oct. 2	Feces	NT	T6, C8, E8	0.1	3.1	50	3.1	0.8	1.6
2	Sept. 30	Bronchus	79/7/54	None	>100	6.3	1.6	6.3	0.8	3.1
	Oct. 21	Trachea	53/77/VA4/73	P3, C20, E20	>100	>100	100	3.1	>100	>100
	Oct. 21	Blood	53/77/VA4/73	P3, C20, E20	>100	>100	100	25	>100	>100
3	Aug. 30	Nose	NT	None	3.1	3.1	1.6	6.3	0.4	3.1
	Oct. 7	Felon	NT	P13, S3	25	6.3	1.6	6.3	0.8	3.1
4	Sept. 21	Rat bite	42B/52/81 ‡	None	25	100	1.6	3.1	0.8	1.6
	Oct. 5	Ulcer	NT	None	25	>100	>100	6.3	>100	6.3
5	Oct. 12	Pleura	54	P10	>100	>100	3.1	3.1	0.4	1.6
	Oct. 24	Subphrenic	47/VA4	P16, T10	>100	>100	>100	3.1	>100	6.3
	Oct. 31	Wound	47/VA4	P16, T17	>100	>100	>100	3.1	>100	6.3
6	Oct. 10	Bone sinus	52A/79	None	50	3.1	1.6	6.3	0.8	3.1
	Oct. 24	Bone sinus	52/52A	C5, E5	50	3.1	1.6	6.3	0.8	3.1
	Nov. 1	Bone sinus	52/52A	C12, E12	25	12.5	3.1	12.5	50	6.3
7	Sept. 1	Wound	42B/52/81	P13, S13	>100	>100	>100	6.3	0.4	1.6
	Sept. 4	Wound	42B/52/81	P13, S13	>100	>100	>100	6.3	0.8	1.6
	Sept. 25	Lung (A) §	NT	P13, S13, T14	>100	>100	>100	12.5	>100	50
	Sept. 25	Spleen (A)	VA4/53/77/42D	P13, S13, T14	0.1	25	1.6	6.3	50	6.3
8	Oct. 10	Furuncle	6/54	S60 ‖	12.5	12.5	1.6	6.3	0.4	1.6
	Oct. 25	Furuncle	42B/52/81/44A	S75	>100	>100	>100	6.3	0.8	3.1
9	Sept. 30	Gall bladder	6/53/77/VA4	None	0.1	6.3	1.6	6.3	0.8	1.6
	Oct. 29	Wound	52	P13, S13	>100	100	>100	6.3	1.6	6.3
10	Oct. 1	Abscess	70	None	0.1	3.1	1.6	6.3	0.8	1.6
	Oct. 14	Abscess	42B/81	P3	0.1	6.3	0.8	6.3	0.8	3.1
11	Sept. 9	Pleura	42B/52/81	P8, S4	>100	>100	>100	6.3	0.8	3.1
	Sept. 18	Pleura	42B/52/81	P10, S4, T2, C6, E6	>100	>100	>100	6.3	0.8	3.1
	Oct. 9	Pleura	42B/52/81	P10, S4, T2, C13, E13	>100	>100	>100	12.5	0.8	3.1
	Oct. 21	Sputum	NT	P10, S4, T2, C13, E13	>100	>100	>100	12.5	>100	50
	Oct. 21	Pleura	42B/52/81	P10, S4, T2, C13, E13	>100	>100	>100	12.5	0.8	3.1
12	Oct. 19	Sputum	NT	None	>100	>100	>100	12.5	>100	50
	Oct. 22	Pleura	NT	None	>100	>100	0.8	12.5	0.8	3.1
	Oct. 31	Pleura	NT	P7	>100	>100	0.8	12.5	0.8	3.1
13	Sept. 28	Blood	42B/52/81/52A, 44A	None	>100	>100	>100	12.5	0.8	3.1
	Sept. 29	Urine	42B/52/81/52A	None	>100	>100	100	12.5	0.8	3.1
	Sept. 30	Blood	42B/52/81/52A	T1	>100	100	>100	6.3	0.8	1.6
	Oct. 1	Subdural	42B/52/81/52A	P1, T1	>100	>100	100	12.5	0.8	3.1
	Oct. 2	Feces	77	P2, T2, C1, E1	>100	>100	100	12.5	0.8	3.1
	Oct. 3	Abscess	42B/52/81/52A	P2, T2, C2, E2	>100	>100	100	12.5	0.8	3.1
	Oct. 14	Blood	NT	P2, T2, C13, E13	>100	>100	100	50	>100	>100

14	Aug. 30	Abscess	52A/79	None	100	12.5	0.8	6.3	0.8	1.6
	Sept. 13	Abscess	54	P1, T10	>100	>100	>100	3.1	0.8	1.6
	Sept. 13	Muscle	NT	P1, T10	>100	>100	50	12.5	0.8	1.6
	Oct. 31	Wound	42B/52/81	P1, T10	>100	>100	100	12.5	0.8	3.1
15	Oct. 13	Blood	57/79/VA4	P7, T23, C9, E9	>100	50	100	6.3	>100	6.3
	Oct. 18	Blood	VA4	P7, T23, C9, E9	>100	>100	100	6.3	>100	3.1
16	Nov. 2	Sputum	42B/52/81/44A	T6	>100	>100	>100	3.1	>100	12.5
	Nov. 12	Blood	42B/52/81	T7, P2, C8, E8	>100	100	>100	12.5	50	100
17	Nov. 3	Pleura	73/VA4	P10, S18	>100	>100	3.1	3.1	0.8	0.8
	Nov. 23	Pleura	54/47/73	P10, S8, C3, E3	>100	>100	3.1	6.3	50	100
	Nov. 27	Pleura	NT	P10, S8, C3, E3	>100	>100	3.1	3.1	0.8	1.6
18	Sept. 3	Pleura	54/47/73/45	P4, S4	>100	>100	1.6	3.1	0.8	1.6
	Sept. 11	Pleura (A)	54/47	P6, S6, T6, C4, E4	>100	>100	50	3.1	0.4	1.6
19	Sept. 2	Wound	NT	P12, S12, T2, E2	>100	>100	>100	3.1	>100	3.1
	Sept. 3	Throat	6/44.4	P13, S13, T3, E3	>100	>100	>100	6.3	>100	1.6
	Sept. 20	Kidney (A)	42B/52 81	P25, S25, T3, E6	>100	>100	0.8	12.5	0.2	1.6

* Italics indicate types in which lysis was weak or occurred only with concentrated phage; NT indicates nontypable.

† P indicates penicillin; S, streptomycin; T, tetracycline; C, chloramphenicol; E, erythromycin; O, oleandomycin; the numbers indicate days of therapy prior to isolation of the strain.

‡ Also reacted weakly with all Group III phages.

§ A indicates autopsy culture.

‖ Received streptomycin and aminosalicylic acid U. S. P. for tuberculosis.

All strains isolated from the same patient were always tested simultaneously. The majority of the changes in susceptibility to antibiotics in successive isolates were of considerable magnitude; such changes were almost invariably associated with the appearance of a strain of a distinctly different phage type. This is illustrated in the strains from Patients 1, 2, 4, 7 (this one showed two such changes), 8, 9, 11, 13, 14, and 17; in all of these patients, except No. 4, 8, and 11, the appearance of a new strain was associated with a change in therapy, the new organisms being resistant to the antibiotics that had been given previously.

Strains that varied grossly in antibiotic susceptibility and phage type were isolated frequently from different sites in the same patient. This occurred in Patients 1, 7, 11, 12, 13, and 19; in Patient 7, two different organisms were isolated at autopsy. These variations were not necessarily related to the immediately antecedent therapy.

Changes in susceptibility of successive isolates of the same phage type were always associated with therapy and tended to consist of relatively minor increases in resistance to one or more of the antibiotics used. Examples of such changes were seen in Patients 6, 16, and 18.

Marked differences in susceptibility to erythromycin in separate isolates were usually associated with similar changes in susceptibility to oleandomycin, as illustrated by the strains from Patients 2, 7, 11, 13, 16, and 17. This was not invariable; for example, in Patients 4, 5, and 7, new strains were resistant to erythromycin but sensitive to oleandomycin.

Finally, there were examples (Patients 6 and 16) of increasing resistance of successive isolates of the same phage type to chloramphenicol, to erythromycin, or to both during simultaneous administration of these two antibiotics. In Patient 6, Staphylococcus of Type 52/52A from osteomyelitis exudate increased markedly in resistance to erythromycin and slightly to chloramphenicol during such combined treatment; this was

accompanied by only a slight increase in resistance to oleandomycin. In Case 16, two strains of Type 42B/52/81 were isolated 10 days apart and the patient received chloramphenicol and erythromycin for 8 of the intervening days. The first strain was sensitive to chloramphenicol and resistant to erythromycin; the second strain showed a fourfold increase in resistance to chloramphenicol, and, although it appeared to be somewhat less resistant to erythromycin, its resistance to oleandomycin had increased eightfold over that of the strain originally isolated.

The findings in Patient 13 are of some interest. In this patient, a nontypable Staphylococcus that was resistant to erythromycin and oleandomycin was isolated from blood after five previous isolations of Type 52/42B/81 and one of Type 77, all of which had been sensitive to these drugs. The final blood culture strain was the most resistant to chloramphenicol of any that were isolated from the 19 patients.

The findings in an additional patient are of interest and are presented in Table 5. On June 17, 1955, this patient had sustained a deep laceration of the right thigh. He was treated by debridement and primary closure and was given penicillin and streptomycin for a month. However, a large hematoma developed in the wound, and an extensive

TABLE 5.—*Antibiotic Susceptibility of Twenty-Nine Separate Isolates of S. Pyogenes Var. Aureus of Phage Pattern 52/52A/80 from Patient with Bacterial Endocarditis* *

Date of Culture †	Previous Therapy, ‡ Days							Minimum Inhibiting Concentration, μg./Ml.						
	P	S	T	C	E	B	N	P	S	T	C	E	B	N
Sept. 11	42	30	22	0	0	0	0	50	6.3	0.8	12.5	0.4	50	0.2
Sept. 26	54	42	22	0	0	0	0	50	100	0.8	12.5	0.4	50	0.2
Oct. 1	59	47	22	0	0	0	0	50	100	0.8	12.5	0.4	50	0.2
Oct. 6	59	47	22	6	6	0	0	25	100	0.8	25	25	50	0.2
Oct. 7	59	47	22	7	7	0	0	50	400	0.8	12.5	25	50	0.2
Oct. 8	59	47	22	8	8	0	0	50	100	0.8	12.5	25	50	0.2
Oct. 10	59	47	22	10	10	0	0	50	100	0.8	12.5	25	50	0.2
Oct. 12	59	47	22	12	12	1	0	25	100	0.8	12.5	25	50	0.2
Oct. 17	59	47	22	17	17	6	0	50	100	0.8	25	25	50	0.2
Oct. 20	59	47	22	20	20	9	0	25	100	0.8	25	6.3	50	0.2
Oct. 21	59	47	22	21	21	10	0	25	100	0.8	25	25	50	0.2
Oct. 22	59	47	22	22	22	11	0	25	100	0.8	25	25	100	0.2
Oct. 23 (a. m.)	59	47	22	23	23	12	0	25	50	0.8	25	25	100	0.2
Oct. 23 (p. m.)	59	47	22	23	23	12	0	25	50	0.8	25	25	50	0.2
Oct. 24	59	47	22	24	24	13	0	50	50	0.8	25	25	50	0.2
Oct. 25	59	47	22	25	25	14	0	50	50	0.8	25	25	50	0.2
Oct. 26	59	47	22	26	26	15	0	25	100	0.8	25	25	50	0.2
Oct. 29	59	47	22	27	27	16	3	50	200	1.6	12.5	50	50	12.5
Oct. 30 (a. m.)	59	47	22	27	27	16	4	50	200	1.6	6.3	50	50	12.5
Oct. 30 (p. m.)	59	47	22	27	27	16	4	50	200	1.6	6.3	50	50	12.5
Oct. 31	60	47	22	27	27	16	5	50	200	1.6	12.5	50	50	12.5
Nov. 12	72	56	22	27	27	16	5	100	200	1.6	6.3	50	50	12.5
Nov. 16	76	60	22	27	27	16	5	100	200	1.6	12.5	25	50	12.5
Nov. 22	77	61	22	32	32	16	5	>100	200	1.6	6.3	25	50	12.5
Nov. 23	77	61	22	33	33	16	5	25	200	1.6	12.5	50	50	12.5
Dec. 22	77	61	22	62	62	16	5							
HB								100	50	1.6	100	12.5	25	12.5
TV								50	100	1.6	100	12.5	25	12.5
RL								25	50	0.8	100	12.5	25	12.5
LL								100	100	1.6	100	12.5	25	12.5

* Complicating an infected wound of the thigh. Phage typing of these strains was done by Dr. John E. Blair; lysis by 52A was variable and often weak.

† All isolations in 1955, and all were from blood cultures except the last 4, which were obtained at autopsy from heart blood (HB) and vegetation of tricuspic valve (TV), right lung (RL), and left lung (LL).

‡ Only the antibiotics given during the present illness are listed; the patient had received penicillin 4 and 9 yr. earlier for other illnesses, and he had also received sulfonamides for 1 wk. prior to date of first culture listed. P indicates penicillin; S, streptomycin; T, tetracycline; C, chloramphenicol; E, erythromycin; B, bacitracin; N, novobiocin. Dosages daily were as follows: P, 2-24,000,000 units (probenecid, 2 gm. daily, given with the larger doses); S, 1-2 gm.; T, 2 gm.; C and E, 2-4 gm. P. O. or 2 gm. I. V. of each; B, 40,000-100,000 units I. M., and N, 2 gm. I. V. or P. O.

staphylococcal infection followed. The wound was incised and drained and then treated by irrigations and instillations of bacitracin and neomycin for several days. Subsequently, there was persistent bacteremia, and changing cardiac murmurs developed. Despite treatment with multiple antibiotics, he died on Dec. 22, 1955. Autopsy revealed verrucous vegetations of the tricuspid valve, multiple emboli with infarcts throughout both lungs, acute glomerulonephritis with multiple hemorrhagic areas, and petechiae and ecchymosis in the skin, conjunctivae, and surface of various organs.

Table 5 summarizes this patient's antibiotic therapy and lists the susceptibility of 29 isolates of coagulase-positive S. pyogenes var. aureus cultured from this patient over a period of nearly three and one-half months. All of these strains were phagetyped by Dr. John E. Blair, of the Hospital for Joint Diseases, New York, and all were found to show exactly the same phage pattern, 52/52A/80. During his illness, the patient had been treated systemically at various times and for varying periods with seven different antibiotics in addition to the topical bacitracin and neomycin used in the wound. If minor fluctuations are disregarded, the following major changes in the susceptibility of the infecting organism were observed:

1. A considerable degree of resistance to streptomycin developed and persisted after the second course of this antibiotic given in combination with penicillin.

2. Some increase in resistance to penicillin may have developed during a later course of this agent that was begun Oct. 31.

3. Resistance to erythromycin developed and persisted after the first six days of treatment with this antibiotic, although it was always given with chloramphenicol; there was no corresponding change in susceptibility to the latter drug. However, the strains isolated at autopsy, after a second course of this combination, showed increased resistance to chloramphenicol.

4. Susceptibility to novobiocin remained unchanged until treatment with this antibiotic was given; resistance to novobiocin then increased sixty-four-fold during the first three days of the five-day course of treatment, and all strains isolated thereafter retained this resistance.

Comment

In general, these observations support the concept that the increasing incidence of staphylococci resistant to various antibiotics is a consequence of the widespread use of antibiotics. However, the mechanism by which resistant strains arise and spread is by no means clear. The present data are consistent with the assumption that the administration of an antibiotic merely alters conditions in the patient so as to permit the implantation or emergence and persistence of strains resistant to that drug. These resistant strains are usually different from those which had been isolated originally and considered to be the etiologic agents of disease in the patient or which had been demonstrated in the absence of evidence of actual disease.

In addition, treatment with certain antibiotics seems to produce increased resistance of originally sensitive organisms in the same patient. While increases of this type usually take place in relatively slow steps, there is evidence that it may develop very rapidly to erythromycin and others of that group and also to novobiocin or streptomycin when these antibiotics are used alone. The findings in the patient with endocarditis complicating wound sepsis, as listed in Table 5, illustrate this very clearly. They show, in addition, that chloramphenicol cannot be relied upon invariably to prevent the development of resistance to erythromycin and that resistance to chloramphenicol itself may also develop in the course of combined treatment.

A possible explanation has been offered for the differences between the infrequent finding of erythromycin resistance among staphylococci of Phage Pattern 52/42B/81; this was based on the strict limitation of the use of this antibiotic within this hospital and the insistence on its use in combination with other active antibiotics. The same facts may serve to explain, in part, the low incidence of chloramphenicol-resistant staphylococci, although the difficulties in inducing high grades of resistance in many staphylo-

cocci by exposures to this antibiotic may be a more cogent factor. Chloramphenicol had, of course, been used extensively for the treatment of infections other than those caused by staphylococci, but it had always been under similar strict control and used relatively infrequently and cautiously at this hospital.

The present findings point to the great need for a more adequate system than the present use of bacteriophage typing for identifying strains that may be changing under the influences of antibiotics or other factors. Perhaps even greater is the need for some measure of virulence and pathogenicity of staphylococci when multiple strains with different susceptibilities to antibiotics occur in the same patient. From a practical point of view it is important to obtain repeated cultures from patients with staphylococcal infections during antibiotic therapy and to study the strains from all possibly infected sites when the patient does not seem to respond to the treatment. Unfortunately, the present findings suggest that, even if this were done, difficulties would still be encountered in interpreting the results. Some of the very irregular and seemingly incongruous results of therapy often encountered in the literature may be due to inadequate study and consequent failure to recognize the intrusion and pathogenic significance of new strains.

Summary and Conclusions

Two hundred ten strains of coagulase-positive Staphylococcus pyogenes var. aureus isolated from infected sources in patients at the Boston City Hospital during the latter part of 1955 were tested for their susceptibility to 18 antibiotics, and one hundred eighty of them were also "phage-typed."

These strains were very uniform in their susceptibility to 10 antibiotics that were new, were not closely related to any of those in common use, or had been available but only rarely used. In contrast, many of the staphylococci were resistant to penicillin, streptomycin, tetracycline, and erythromycin and to three related drugs, oleandomycin and spiramycin (which are related to erythromycin) and synnematin B (closely related to penicillin). Chloramphenicol was the only widely used antibiotic to which few of the strains were resistant.

A considerably greater proportion of the strains resistant to penicillin, streptomycin, tetracycline, and erythromycin were isolated from patients during or after treatment with antibiotics.

Staphylococci of Phage Pattern 52/42B/81 constituted about one-third of the total; slightly more than one-fourth of the strains were nontypable with the phages used, and the rest of the strains were lysed by phages of a large number of single types or patterns.

Staphylococci of Type 52/42B/81 differed from all others in their susceptibility to penicillin, streptomycin, tetracycline, and erythromycin; nearly all of them were resistant to the first three but sensitive to erythromycin. A considerable proportion of the nontypable strains and of those lysed by other phages were resistant to penicillin, streptomycin, and tetracycline, and a smaller number were resistant to erythromycin.

Data were presented on multiple strains of staphylococci isolated from patients during the course of infection and on changes in their susceptibility to antibiotics. Most of the marked differences were related to the introduction or recognition of new strains of different phage types and probably represented mixed infections or superinfections; these new strains were usually, but not always, highly resistant to all of the antibiotics that were being used in the patients from whom they were isolated. Occasional decreases in susceptibility to antibiotics were noted in successive isolations of staphylococci of the same phage pattern; in general, these were clearly related to the antibiotics in use.

Thorndike Memorial Library, The Boston City Hospital, 818 Harrison Ave. (18).

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Penicillin Sensitivity of Gram-Negative Enteric Bacilli

Successful Treatment of Urinary Tract Infections

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Of the Gram-negative flora, those really sensitive to penicillin are the Neisseriae, which behave chemotherapeutically the same way as the Gram-positive cocci. If we modify our definition of sensitivity and go to higher concentrations than those usually attained in the body after the clinical dosage forms of penicillin, we may encounter a few strains that are inhibited by moderate concentrations of the antibiotic. There are a few reports in the literature of septicemias caused by Gram-negative resistant bacteria (as Proteus) that were cured by huge doses of penicillin.[2-5,9]

The minimal inhibitory concentrations for those strains were mostly 10μg.-20μg. per milliliter. Strains requiring higher concentrations have been correctly considered as extra resistant. Attention has been drawn to the sensitivity of Proteus, and the strains of Proteus mirabilis have been proven more sensitive than the other strains.[1,6,7,9]

The concentrations used in those studies were very low (3μg. per milliliter). The same results were reported more recently by other investigators,[10] who found also a few strains of other enteric Gram-negative bacilli sensitive to penicillin (Escherichia coli, Aerobacter aerogenes, Pseudomonas species). No change in sensitivity between strains of E. coli and strains of A. aerogenes, isolated in 1951-1952 and in 1955, was observed by the last investigators.[10]

The problem of the urinary tract infections that resist the usual chemotherapy is growing in importance every day. In an effort to tackle it, we set out testing Gram-negative organisms for sensitivity to high concentrations of penicillin. We used for initial screening tests paper disks prepared in our laboratory. A smaller number of strains, especially of those cases that were subjected to penicillin treatment, was examined for the minimal inhibitory concentration on the antibiotic by the broth serial-dilution method. Knowing the high concentrations attained in the urinary tract by relatively small doses of penicillin, we attempted the treatment of infections caused by micro-organisms sensitive to high concentrations of the drug. Some of those infections presented therapeutic problems because the strains were resistant to other antibiotics. Our results confirmed our expectations.

Materials and Methods

All of the strains tested have been isolated from clinical material at the Research Laboratory of the Athens University Department of Clinical Therapeutics (Alexandra Hospital) from February, 1958, through August, 1958. The patients were either hospitalized or outpatients referred to us for consultation and laboratory evaluation by their physicians.

Enriched nutrient broth, blood agar, MacConkey agar, and thioglucolate broth were used as culture media.

Urine cultures were made in the females from catheterization urine and in the males after proper cleaning of the urethral meatus. Usual contaminants were not tested. All of the strains used were from cases with active infection as judged by the

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great numbers of viable organisms counted by pour-plate technique (over 100,000 per milliliter).

Antibiotic sensitivity studies were conducted at first by homemade disks for screening and subsequently by serial dilutions in liquid media. The disks were made to contain 6μg. and 60μg. of penicillin per disk. They were kept in 40 C in tightly screwed containers not longer than four weeks after their preparation. Potency was assured by control studies on known sensitivity strains by both methods (disks and tube serial dilutions) for each batch.[11] Serial twofold dilutions were made in broth. The 12- to 16-hour cultures were diluted in broth to the 10^{-3} to 10^{-4}. Bactericidal action, and not simply bacteriostatic, was read.

Penicillinase production was examined by the Heatley cylinders method. The results were expressed as 1+, 2+, 3+, and 4+, according to the inhibition zone as compared to the zone produced by the cylinder containing only penicillin.

Urine penicillin levels were tested in a few patients by the serial-dilutions method in broth. As test organism for the assays the Oxford strain of Staphylococcus pyogenes var. aureus was used.

Results

Laboratory Studies.—By the disk method (content of each disk, 60μg. of penicillin), 250 strains of Gram-negative enteric bacteria were tested for sensitivity. Of the 250 strains, 72 proved sensitive to penicillin in that high concentration. We have not been able to test all strains for exact sensitivity by the serial-dilutions method. Of the 250 strains, 126 strains were E. coli; 58 strains, Klesbiella pneumoniae; 40 strains, Proteus species; 22 strains, Pseudomonas aeruginosa, and 4 strains, Alcaligenes faecalis. Thirty-one of these strains that proved sensitive to penicillin by disks were subsequently examined for the exact minimal inhibitory concentration and penicillinase production. The results are given in Table 2. Of the 31 strains, 13 belonged to cases which have been successfully treated by penicillin, as described later in the case reports.

TABLE 1.—*Penicillin Sensitivity of 250 Gram-Negative Bacilli* *

	Strains, No.	Sensitive in Penicillin
Escherichia coli	126	52
Klebsiella pneumoniae	58	13
Proteus species	40	5
Pseudomonas aeruginosa	22	0
Alcaligenes faecalis	4	2
Total	250	72

* Sensitivity was checked by the disk method. Homemade disks contained 60μg. per disk. Exact determination of the minimal inhibitory concentration was conducted in 31 strains.

TABLE 2.—*Minimal Inhibitory Concentration and Penicillinase Production of Thirty-One Strains of Bacteria*

Patient No.	Source	Bacterial Species	M. I. C. of Penicillin, μg/Ml.	Penicillinase Production
1	Urine	Escherichia coli	7.5	+
2	Urine	Escherichia coli	15.0	+
3	Urine	Escherichia coli	30.0	+
4	Urine	Escherichia coli	30.0	+
6	Urine	Escherichia coli	30.0	++
7	Urine	Escherichia coli	30.0	+
8	Urine	Escherichia coli	30.0	0
9	Urine	Escherichia coli	30.0	+
10	Urine	Escherichia coli	30.0	+
11	Urine	Escherichia coli	30.0	+
12	Urine	Escherichia coli	30.0	+
13	Urine	Escherichia coli	30.0	0
14	Urine	Escherichia coli	30.0	+
15	Sputum	Escherichia coli	30.0	+
16	Sputum	Escherichia coli	30.0	++++
17	Feces	Escherichia coli	30.0	+
18	Urine	Escherichia coli	60.0	+
19	Sputum	Escherichia coli	60.0	0
20	Urine	Escherichia coli	60.0	+
21	Sputum	Escherichia coli	60.0	++++
22	Bile	Escherichia coli	120.0	++++
23	Urine	Proteus	7.5	0
24	Urine	Proteus	7.5	0
25	Sputum	Klebsiella	60.0	+
26	Sputum	Klebsiella	60.0	++++
27	Urine	Klebsiella	30.0	+
28	Sputum	Klebsiella	30.0	+
29	Urine	Escherichia coli	30.0	+++
30	Urine	Escherichia coli	30.0	+++
31	Urine	Escherichia coli	30.0	+++

TABLE 3.—*Analysis of Sixteen Cases of*

No.	Age, Yr.	Sex	Clinical Picture	Laboratory Findings	Causative Organism
1	34	M	High fever, cystitis	Leukocytosis, pus cells +++	E. coli
2	63	M	High fever, cystitis	Leukocytosis, pus cells +++	E. coli
3	40	F	High fever of 40 day's duration, cystitis	Leukocytosis, pus cell, casts ++++	E. coli
4	58	F	Fever, cystitis	Leukocytosis	E. coli
5	30	F	High fever, asymptomatic	Leukocytosis	E. coli
6	57	F	Fever, hematuria for 6 mo.	Leukocytosis +++, pus cells +++, casts +++	K. pneumoniae
7	35	F	Low-grade fever, cystitis	Pus cells ++	E. coli
8	40	M	Asymptomatic	Pus cells ++	E. coli
9	65	F	Asymptomatic	Pus cells +++	E. coli
10	36	F	Low-grade fever, cystitis	Pus cells +++	E. coli
11	31	F	Low-grade fever, post partum	Pus cells +++	E. coli in urine & vaginal discharge
12	70	F	Low-grade fever, cystitis	Masses of pus cells	E. coli
13	44	M	High fever, kidney colics, hematuria	Leukocytosis, hematuria, pus cells ++++	P. mirabilis
14	40	M	Pneumonia	Leukocytosis, purulent sputum	Klebsiella
15	45	F	Pneumonia	Leukocytosis, hematuria, pus cells ++++	Klebsiella
16	45	F	Low-grade fever, post partum	Vaginal purulent discharge	K. pneumonia (vagina)

As seen in Table 1, the minimal inhibitory concentration (M. I. C.) ranged from 7.5μg. per milliliter (three strains) to 120μg. per milliliter. For 5 strains the M. I. C. was 60μg. per milliliter; for 9 strains, the M. I. C. was 30μg.; for 1 it was 15μg.

Of the 31 strains, 24 were E. coli, 2 were Protei, 5 were K. pneumoniae.

Penicillinase production was detected in seven strains showing the maximum of production (4+), of which six were E. coli and one Klebsiella. In another strain of Klebsiella, penicillinase production was moderate (2+), and in 17 strains, minimal (1+). Of the 17 strains with minimal penicillinase production, 13 were E. coli and 4 Klebsiella. Penicillinase production cannot be strictly correlated with the minimal inhibitory concentration of penicillin because two of the great producers required a M. I. C. of 60μg., another one, 120μg., and a fourth one, 30μg. per milliliter. For the moderate producers the correlation was more difficult. On the other end the more sensitive strains with a M. I. C. of 7.5μg. per milliliter did not produce penicillinase, except for one strain which produced a minimal amount.

Clinical Observations.—Table 3 presents an analysis of the results of penicillin treatment of 16 cases with infections caused by micro-organisms proven sensitive to high concentrations of penicillin.

Of the 16 cases, 13 were urinary tract infections with varying symptomatology, most with fever and overt signs of cystitis. Eleven of the thirteen were caused by E. coli; one, by P. mirabilis, and another one by K. pneumoniae. One case (No. 11) presented urinary tract infection and genital tract infection, the same strain being isolated from urine and vaginal discharge. Two cases of pneumonia and a case of genital tract infection caused by Klebsiella were treated unsuccessfully by high doses of penicillin (No. 14, 15, and 16). Apparently the levels of the antibiotics were not high enough to reach the minimal inhibitory concentration for the causative micro-organisms.

The results in all 13 cases of urinary tract infections were excellent. Clinical improvement was prompt (within the first or second day), followed by laboratory cure. The cultures became negative within two to three days after treatment, with only one excep-

Gram-Negative Infections Treated with Penicillin

Penicillin Minimal Inhibitory Concentration, μg/Ml.	Penicillinase Production	Penicillin Dosage, Million Units/24 Hr.	Effect on Symptoms	Effect on Urinary Culture Days of Negativity After Treatment
15	+	5.6	Afebrile in 24 hr.	Clear in 48 hr.
7.5	+	1.6	Afebrile in 24 hr.	Clear in 48 hr.
30	+	5	Afebrile in 48 hr.	Clear in 8 days, culture negative 18th day, temporarily
		10		
30	+	1.6	Afebrile in 48 hr., asymptomatic	Clear, negative in 48 hr.
30	+	2.4	Afebrile 24 hr., asymptomatic	Clear, negative in 24 hr.
60	+	3	Afebrile 24 hr., asymptomatic	Clear, negative in 48 hr.
30	0	4.6	Asymptomatic, afebrile in 48 hr.	Clear, negative in 48 hr.
30	0	3	—	Clear, negative in 48 hr.
60	+	5.6	—	Clear, negative on 2d day
30	+++	6	Afebrile on 2d day, asymptomatic	Clear, negative on 3d day
30	+++	6	Afebrile on 3d day, asymptomatic	Clear, negative on 3d day
30	+++	6	Afebrile on 3d day, asymptomatic	Clear, negative on 3d day
75	0	5	Afebrile, asymptomatic in 48 hr.	Negative, clear in 3 days
30	+	10	No effect	No effect
60	++++	10	No effect	No effect
		5	No effect	No effect

tion (No. 3). The causative strains ranged in sensitivity from 7.5μg. to 60μg. per milliliter. The majority did not produce penicillinase. Only three strains produced moderate amounts, but this did not interfere with the good result of the treatment.

The doses of penicillin used ranged from 1,600,000 units daily (two cases) to 10,000,000 units daily (three cases); all regimens used proved effective. Penicillin levels in the urine were not measured in all cases because of lack of cooperation by the patients. In three cases the level exceeded by far the minimal inhibitory concentration for the causative strains.

We give detailed reports of four cases that present particular interest.

Report of Cases

CASE 1.—A 34-year-old man entered the hospital with high fever and symptoms of cystitis, which preceded the fever by three days. Leukocytosis (12,000 WBC) was found. Urine examination revealed many pus cells. Urine culture gave abundant growth of E. coli, sensitive by the disk more to penicillin and much less to streptomycin, chloramphenicol, and nitrofurantoin (Furadantin). The strain was completely inhibited by 15μg. of penicillin per milliliter. Aqueous solution of crystalline penicillin G was administered I. M., in a dose of 5,600,000 units daily (divided in four doses). Within 24 hours after institution of treatment the fever and the urinary bladder symptoms subsided. The urine culture became negative after two days. The patient was in a hurry to be discharged on the third day of treatment, after which he discontinued penicillin. In another five days he experienced a recurrence of the fever and of the cystitis symptoms. He entered the hospital again, and the urine culture was positive for E. coli of the same sensitivity. After one day of penicillin treatment (the same dose as before) he became afebrile again and free of symptoms. Urine culture became negative in 24 hours. Treatment was continued for a week. He had no recurrence during two months of observation, and the urine culture was still negative after two months.

CASE 2.*—A 40-year-old woman had been hospitalized, at the Naval Hospital of Athens, with fever and urinary symptoms, for 40 days. She received almost all antibiotic therapy available. In repeated urine cultures E. coli was isolated, resistant to all antibiotics tested. Her illness had started six months earlier, with fever and cystitis symptoms. E. coli was isolated from the urine, sensitive to oxytetracycline, which was administered successfully. After one month she had a recurrence. Nitrofurantoin was used successfully. After two months signs and symptoms recurred. E. coli was

* Dr. Jachnis, of the Medical Service of the Athens Naval Hospital, gave permission to use this case.

again isolated from the urine. Sulfamethoxypyridazine and nitrofurantoin were used successively. After discontinuation of the drugs, she experienced a new recurrence and was admitted to the Naval Hospital, where all available antibiotics were tried, with no success. The strains continued being resistant to all chemotherapeutics tested. We were called for consultation, and we also isolated the same strain of E. coli, which was tried for sensitivity to penicillin. It proved sensitive to 30μg. per milliliter. Leukocytosis (15,000 WBC) and all the signs of infection were present. Penicillin therapy was instituted before the exact determination of the minimal inhibitory concentration. A dose of 5,000,000 units daily (in three doses) of aqueous crystalline penicillin intramuscularly was started. The fever and the symptoms subsided within 24 hours, for the first time in 40 days. Urine cultures gave much smaller numbers of E. coli colonies, but they remained positive despite the large doses of penicillin. After four days we increased the dose to 10,000,000 units daily. Penicillin was continued for 20 days because in some cultures a few colonies of E. coli occasionally appeared. Urine penicillin levels were on several occasions above 200μg. per milliliter. After discontinuation of penicillin, the patient remained free of symptoms and signs of infection but the urine culture became positive again and abounded in E. coli. A search for mechanical or other reasons favoring the perpetuation of the infection proved fruitless except for a persistent constipation. Repeated urine cultures gave abundant growth of E. coli.

In this case no chemotherapeutic was able to eradicate the infection other than penicillin, which proved lifesaving.

Case 3.—A 44-year-old man entered the hospital with a high fever and colic of the left kidney. Urine examination revealed hematuria, many pus cells, and a few hyaline and granular casts. WBC was 12,000. Urine culture gave abundant growth of P. mirabilis, resistant to all antibiotics except penicillin (7.5μg. per milliliter). After two days of penicillin treatment (5,000,000 units daily) he became afebrile and free of symptoms. The urine culture was negative within 48 hours and remained so for two months with no recurrence. The strain did not produce penicillinase. Penicillin levels in urine were above 50μg. per milliliter the second day of treatment (three hours after penicillin injection).

Case 4.—A 31-year-old woman entered the hospital with a low-grade fever 20 days post partum. Urine sediment gave abundant pus cells. Urine culture grew high numbers of E. coli sensitive to penicillin (30μg. per milliliter), sulfamethoxypyridazine, and nitrofurantoin. Penicillinase production of the strain was 3+. Crystalline penicillin G was administered I. M. in a dosage of 6,000,000 units daily, divided in three equal doses, for a week. Clinical cure was accompanied by negative culture within two days of treatment. Urine penicillin levels were above 60μg. the second day of treatment (three hours after injection). Interestingly enough, the same strain of E. coli was isolated from the vagina. Despite the penicillin treatment, repeated cultures of vaginal secretions kept growing E. coli. The fact is easily explained by the different concentrations of the antibiotic in the urinary tract and vagina. The levels at the latter are much lower, not reaching the minimal inhibitory concentration for the particular strain concerned (30μg. per milliliter).

Comment

The problem of bacteria which are resistant to all chemotherapeutic agents becomes very acute in several cases. Any contribution to the solution of it is welcomed by the often helpless clinician. Penicillin in the usual concentrations attained in the body proves ineffective against the so-called enteric Gram-negative bacteria. As seen in the present report, there are several strains that can be completely inhibited by larger doses of penicillin. Of that fact there are a few reports in the literature. Concentrations high enough to inhibit the growth of several bacterial strains (such as those we isolated) can be built up in the organism, but with great difficulty. In the urinary tract, though, we have a high concentration of the antibiotic with smaller doses, well beyond the minimal inhibitory concentration required by bacteria like the ones we have isolated.

Our findings are of great significance, especially for urinary tract infections. Of 250 strains of Gram-negative bacteria of the enteric group, 72 have proved sensitive to penicillin concentrations which can easily be obtained in the urinary tract. Several of them (seven) were resistant to other chemotherapeutics.

The clinical and bacteriologic cure, as seen in our cases, seems to be obtained with relatively small daily doses. The maximum required was 10,000,000 units. In two cases, 1,600,000 units proved sufficient; in another two, 3,000,000 units, and in one 2,400,000 units.

Bacteriologic cure was long lasting except in one case (No. 3), which, as generally observed, might have been mechanical or had other reasons favoring the bacteriuria. The infection, though, was overcome in all cases, including that one with the persisting bacteriuria.

Penicillinase was not produced by all strains, but it did not seem to matter even in the ones that had a great production. The capability of a strain to produce penicillinase is usually closely connected with resistance to penicillin. It seems that the definition of resistance needs qualification, because we usually mean the sensitivity of a higher than 5μg.-10μg. per milliliter concentration. In our strains, great penicillinase production was observed where the M. I. C. was above 30μg. per milliliter.

In the strains that showed a great penicillinase production the sensitivity remained.

Most probably the final effect of penicillin inhibition and penicillinase action depends on the killing rate of penicillin and on the penicillinase production rate. The latter is not so fast as to interfere with the action of penicillin in such great concentrations. The amount of the penicillinase produced is not of such an order as to neutralize as large doses of penicillin as the ones involved in our strains.

The failure to cure pneumonia caused by strains of sensitivity of the order of 30μg.-120μg. per milliliter is due to the difficulty of attaining such levels in tissues, namely, the lungs. The dose required for that purpose is far greater than the ones used.

Of special interest are the two cases (Nos. 11 and 16) with positive vaginal cultures (vaginitis) even after large doses of penicillin. Apparently the level in the vagina did not reach the M. I. C. for the causative strains. In the one case (No. 11) the same organism was eradicated from the urinary tract while persisting in the vagina.

The negative results in pulmonary and genital infections proves that it is not possible to eradicate bacteria sensitive to such high concentrations of penicillin from parts other than the urinary tract. There are reports in the literature[3-5,8,9] of cure of septicemias due to resistant bacteria (mostly Proteus) sensitive to high concentrations of penicillin. The doses used in those cases were of a much higher order than the ones which proved sufficient in the urinary tract infections caused by micro-organisms of a similar penicillin sensitivity.

Summary

The in vitro penicillin sensitivity of 250 strains of enteric bacilli was examined by use of homemade disks (60μg. per disk). Of the 250 strains, 72 proved sensitive to that high concentration of penicillin. Of 126 Escherichia coli, 52; of 58 Klebsiella pneumoniae, 13; of 40 Proteus, 5; of 4 Alcaligenes faecalis, 2, and of 22 Pseudomonas aeruginosa, none were inhibited by 60μg. per milliliter of penicillin.

In 31 strains the exact minimal inhibitory concentration was determined by the tube serial-dilution method. Of the 31 strains, 24 were E. coli, 2, Proteus and 5, Klebsiellae. The minimal inhibitory concentration was for the majority of strains 30μg. per milliliter (19 strains). For five, the minimal inhibitory concentration (M. I. C.) was 60μg.; for three, it was 7.5μg.; for one, 120μg., and for another one 15μg. per milliliter.

Penicillinase production was marked in 7 of the 31 strains; in the rest it was negligible. No correlation was possible between penicillinase production and minimal inhibitory concentration.

Clinical studies in 13 cases of urinary tract infections caused by 13 of the above 31 bacterial strains studied showed dramatic effects after penicillin treatment. The doses used ranged from 10,000,000 units to 1,600,000 units daily (I. M., crystalline aqueous form). Two cases of pneumonia and two of gynecological infection caused by bacteria of the above group of 31 did not respond favorably to penicillin.

The advisability of testing urinary tract isolates for penicillin sensitivity is discussed.

In case the strain proves sensitive up to 120μg. per milliliter of penicillin (or even more), the treatment with that antibiotic is effective and recommended. In some of our cases penicillin proved to be the only effective chemotherapeutic. The favorable results are apparently due to the high penicillin levels attained in the urinary tract even with moderate or relatively small doses of the antibiotic.

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Addendum

After completion of the present paper, we had occasion to test 30 additional strains of E. coli, 5 strains of Proteus, and 7 strains of P. aeruginosa. Seven of the E. coli proved sensitive to 60μg. of penicillin (disk method).

We also had the opportunity to treat another patient, who had acute pyelocystitis due to E. coli, which proved sensitive to chloramphenicol and penicillin (30μg. per milliliter by serial-dilution method). The patient had received chloramphenicol with only temporary success. She responded immediately to 6,000,000 units of penicillin I. M. daily, and the urine culture became negative the second day of treatment, remaining so at repeated checking thereafter.

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Relative Polycythemia

Alterations of Red Cell Distribution Simulating Hemoconcentration

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A high concentration of red cells in the venous blood, as indicated by hematocrit, red cell count, or hemoglobin concentration, is likely to be accepted as evidence of an increased amount of circulating red cells. An increased amount of circulating red cells may be a primary disorder (polycythemia vera), or it may be secondary to cardiopulmonary disease or low environmental oxygen tension.[1]

It is possible to have a high concentration of red cells in the venous blood without an increase in total red cell volume. A group of such patients, studied by Lawrence and Berlin,[2] was found to have some of the symptoms of polycythemia vera: ruddy complexion, headache, easy fatigability, dizziness, etc. The total circulating red cell volumes were measured with radioactive phosphorus-labeled red cells and were found to be within normal limits, even though the venous hematocrits were greater than 50%. Since these findings are incompatible with a true polycythemia in the absence of hemorrhage,[3] another explanation for this discrepancy was sought. Plasma volume was calculated in these patients and was found to be reduced below the range of normal in every case. It was concluded, therefore, that the high concentration of red cells in the venous blood was a result of a reduction in plasma volume (hemoconcentration) rather than an expansion of the red cell volume. The term "relative polycythemia, the polycythemia of stress" was used to describe this condition, since there was evidence of emotional stress in some of the patients.

A selected group of patients, similar in many details to those studied by Lawrence and having an initial diagnosis of polycythemia, has been studied in our laboratory. Radioactive chromium labeled red cells were used to measure total red cell volume, a method accepted as equivalent to the radiophosphorus technique.[4] Red cell volumes were not enlarged in these patients. Plasma volume was calculated from the total red cell volume and the venous hematocrit according to the method of Lawrence and Berlin. In every instance it was found that plasma volume calculated in this manner was less than normal (Column 3, Table), thus substantiating in every detail the reported findings of a polycythemia due to a reduction of plasma volume, that is, a relative polycythemia.

There is, however, some question as to the validity of this method of calculating plasma volume. Implicit in this method is the assumption that the venous hematocrit is equal to the total-body hematocrit, although considerable evidence indicates that such is not the case.[5-7] Despite this evidence, Lawrence, in a recent publication, states, "We do not believe that the total-body hematocrit is significantly different from the venous hematocrit, and we feel that the plasma volume can be calculated with a high degree of precision from the total red cell volume and the venous hematocrit."[4]

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Case Summary

Case	Column 1 Venous * Hematocrit	2 Red Cell Vol., Cc/Kg.	3 Calculated Plasma Vol., Cc/Kg.	4 Measured (Risa) Plasma Vol., Cc/Kg.	5 Total Blood Vol., Cc/Kg.	6 Total Body Hematocrit, Col. 2/Col. 5	7 Ratio Total Body Venous Hct.	8 Body Weight, Kg.
1	51	25.8	24.8	31.4	57.1	45	0.88	86.4
2	59	31.8	22.1	24.6	56.4	56	0.95	75.0
3	62	24.5	15.0	29.8	54.4	45	0.73	69.5
4	54	22.4	19.1	33.5	55.9	40	0.74	71.4
5	55	29.7	24.3	45.4	75.1	40	0.73	71.4
6	54	31.4	26.7	37.9	69.3	45	0.83	76.4
7	51	22.0	21.1	31.2	53.2	41	0.80	89.1
8 †	52	28.2	26.0	41.0	69.2	40.7	0.78	68.1
9 †	56	27.9	21.9	36.6	64.5	43	0.77	60.0
10	19	34.6	431.8	66.7	101.3	34	1.79	75.9

* Uncorrected for trapped plasma.

† Permission to use these data was granted by Dr. R. J. Poppiti, North Broward General Hospital, Fort Lauderdale, Fla.

To test the validity of Lawrence's hypothesis and, therefore, the existence of such a "relative polycythemia," we measured plasma volume in these patients by use of radioactive serum-albumin-dilution determinations of plasma.

Method

Total red cell volume was measured by tagging the patient's red cells with 50μc. of Cr^{51}, with use of Read's* sodium ascorbate technique to "freeze" the labeling process, and later correcting for the supernatant chromium in the tagged material and in the final blood sample. When the final Cr^{51} blood sample was drawn (45 minutes after the labeled red cells were injected), 10μc. of I^{131}-labeled human serum albumin was injected. A sample of blood was drawn 10 minutes later for measurement of the volume of dilution of the labeled protein (plasma volume). A suitable correction was made for Cr^{51} circulating in the plasma at that time as determined from the 45-minute CR^{51} blood sample.

Results

In only two cases could we predict the plasma volume by calculation from the total red cell volume and the venous hematocrit with an error of less than 30% (Column 3 *vs.* Column 4). It follows that the venous hematocrit does differ appreciably from the total-body hematocrit, and we conclude that plasma volume cannot be calculated from the total red cell volume and the venous hematocrit. Since we have measured both total red cell volume and plasma volume, we can calculate the total blood volume (their sum) and the total-body hematocrit (total red cell volume/total blood volume, Columns 5 and 6). In all of these cases, the total-body hematocrit was less than the venous hematocrit (Column 7). It has been our experience that the total-body hematocrit-to-venous hematocrit ratio approximates 0.9. This group of patients, with the exception of Case 1 and Case 2, is unusual in that this ratio is very low, indicating an atypical distribution of red cells. Case 2 is an example of true hemoconcentration; the plasma volume is greatly reduced, whereas the total red cell volume is normal: a "relative polycythemia." Although the plasma volume is moderately reduced in Cases 1, 3, and 7, there is a corresponding reduction in the total red cell volume, and so the net result is not a hemoconcentration. The remaining patients had an absolute increase in their plasma volume.

Comment

In the absence of an expansion of the total red cell volume, a reduction in plasma volume is not the only cause of a high venous hematocrit. If one accepts the fact that the venous hematocrit is not always representative of the total-body hematocrit, there is no need to postulate absolute volume alterations to account for hemato-

crit changes. The work of Gibson et al.[9] demonstrates that the hematocrits of different organs vary from 15% in the small vessels of the kidney to 82% in the spleen. This conforms to the hydrodynamic theory [10] that the concentration of particles in a suspension flowing through a series of pipes will be a function of the diameter of the pipes and the velocity of flow. There is considerable evidence that the usual ratio of total-body hematocrit to venous hematocrit in man is 0.9.[5-7,11] This has been our experience as well.

The alteration in this ratio which occurs in congestive splenomegaly has been the subject of several publications.[12,13] Since, in congestive splenomegaly, a large volume of high-hematocrit (splenic) blood contributes to the total-body hematocrit, the latter will be greater than the venous hematocrit. Rothschild et al.[12] differentiated the congested from the fibrotic spleen on the basis of a total-body hematocrit-to-venous hematocrit ratio greater than one. Case 10, in which there was massive splenomegaly, illustrates the extreme of such a situation, in which the venous hematocrit is 19% in the presence of an expanded red cell volume.

Most of the cases in this group of suspected polycythemia present findings which are the reverse of those seen with splenomegaly. The ratio of total-body hematocrit to venous hematocrit is reduced below 0.9 because of a shift of red cells to the large vessels. This results in an elevated venous hematocrit and gives a spuriously high indication of the total-body hematocrit, if the venous hematocrit is considered alone. Whether this is due to a reduction in the volume of a high-hematocrit compartment and/or an increase in the volume of a low-hematocrit compartment is not apparent from our data, but hemoconcentration plays no role.

Most of our patients had marked flushing of the skin. In man, the skin is a large and vascular organ capable of wide fluctuations in its blood supply. This merits further investigation as a mechanism for a shift of red cells which appears as polycythemia.

Summary

Independent total red cell volume and plasma volume measurements were done on a group of patients with a tentative diagnosis of polycythemia. Although they all had a high venous hematocrit, none had an increased total red cell volume. Since these patients had many of the symptoms of polycythemia, these symptoms may be related to the high venous hematocrit that these two disorders have in common. Our data demonstrate that it is not valid to calculate plasma volume from the total red cell volume and the venous hematocrit. The plasma volume must be separately determined. Although the ratio of total-body hematocrit to venous hematocrit is usually 0.9, there are conditions which alter it strikingly, giving a false impression of polycythemia. Plasma volume measurements suggest two mechanisms for a high venous hematocrit without polycythemia: (1) a reduction in the plasma volume, (2) a shift in the distribution of red cells. The cause(s) of these changes is not apparent from this study.

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Appendix

Case 1.—A 59-year-old man with arrested tuberculosis was hospitalized in October, 1957, for hypertension, progressive weakness with exertional dyspnea and anginal chest pain, and melena. One year previously, slight hepatomegaly was noted; hematocrit then 41%, hemoglobin 12.5 gm/100 ml., and WBC 12,000 per cubic millimeter, with normal differential. Blood pressure now 188/98; he was obese and plethoric, without palpable liver or spleen. Hematocrit varied from 44% to 51%, with maximum hemoglobin of 15.5 gm/100 ml. WBC varied from 7,850 to 11,900 per cubic millimeter, with slight but persistent lymphocytosis and 14% band cells on one occasion. Highest platelet count was 220,000 per cubic millimeter; reticulocytes, consistently below 1%. Other significant data: Sulfobromophthalein (SBP) retention was 6%; uric acid, 6.05 mg/100 ml., total cholesterol, 365 mg/100 ml. (esters, 213 mg/100 ml.), fasting blood sugar, 113 mg/100 ml. Urinalyses were normal. Stools were consistently guaiac-positive, but gastrointestinal x-rays showed no lesions. Radioiodine uptake was 17% in 24 hours; radioiron turnover rate and red cell synthesis rate, less than normal. Serum iron was 0.080 mg/100 ml.

Case 2.—A 62-year-old retired dentist was admitted because of prostatic carcinoma and probable left retinal hemorrhage. Chief complaint was "blood count too high." Past history included frequent headaches, a peptic ulcer, and a severe emotional strain. One son had chronic granulocytic leukemia. Blood pressure was 170/100. The mucosae were deeply colored but not cyanotic; the face was "flushed." The heart was not enlarged; neither liver nor spleen was palpable. Laboratory data: Hemoglobin varied from 15.5 to 16 gm/100 ml.; hematocrit was up to 55%; red cell count, up to 6,500,000 per cubic millimeter; WBC, 7,800, with normal differential; platelets 220,000 per cubic millimeter. Urinalyses were normal. Two-hour postprandial blood sugar was 167 mg/100 ml.; acid phosphatase, 3.2 Gutman units/100 ml. Chest x-ray was normal.

Case 3.—A 48-year-old office clerk was admitted for objective vertigo with tinnitus, nausea without emesis, and paresthesias. The patient was informed in 1945 of "some abnormality of the blood cell producing organs," but no details were available. Complexion was ruddy; blood pressure was 130/100. Heart was not enlarged, and neither liver nor spleen was felt. Neurological examination was negative. Laboratory data: Hematocrit varied from 56.5% to 62%; hemoglobin varied from 16 to 17 gm/100 ml; WBC varied from 12,600 to 13,350 per cubic millimeter, with 3% basophils; platelets were 204,000 per cubic millimeter. Urinalyses were negative. Uric acid was 1.7 mg/100 ml.; BUN, 23 mg/100 ml. Sternal bone marrow showed slight erythroid hyperplasia.

Case 4.—A 40-year-old man was hospitalized several times for bleeding peptic ulcer. He was admitted in July, 1957, for uncontrollable epistaxis with dizziness. Blood pressure was 110/75; liver and spleen, not palpable. Hemoglobin was 15 gm/100 ml.; hematocrit, 50%; WBC, 16,000 per cubic millimeter, with normal differential; platelets, 150,000 per cubic millimeter. Capillary bleeding time and venous coagulation time were normal. The epistaxis was easily controlled in the hospital. One year previously, hemoglobin was 16.5 gm/100 ml. and hematocrit was 54%.

Case 5.—A 71-year-old man was admitted on several occasions. The patient had bled excessively for years following minor trauma and also after a subtotal gastrectomy, done in 1955, for a bleeding duodenal ulcer. In June, 1956, a draining abdominal sinus was excised. Blood pressure was then 140/70; both liver and spleen were palpable. Hemoglobin was 10.5 to 13.5 gm/100 ml.; hematocrit, 37% to 48%; WBC, 33,800 to 67,400 per cubic millimeter, with mature neutrophils predominating; reticulocyte count, 1.4%; platelets were 226,000 per cubic milli-

meter; both bleeding and coagulation time, moderately prolonged. Bone marrow showed generalized hyperplasia. Diagnosis at that time was chronic granulocytic leukemia *vs.* leukemoid reaction or polycythemia vera. The patient was readmitted in June, 1957, because of tenseness, temper outbursts, and one convulsion. He later developed left-sided weakness. Both liver and spleen were still enlarged. Clinical impression was brain abscess or thrombotic episode. WBC had risen to 74,000 to 102,000 per cubic millimeter, with normal differential; hemoglobin was 14.4 gm/100 ml.; hematocrit, 49%; alkaline phosphatase, consistently elevated. Uric acid was 9.8 mg/100 ml. Autopsy, July, 1957, showed astrocytoma, Grade 3, in right frontal lobe and changes consistent with chronic granulocytic leukemia.

CASE 6.—A 42-year-old man was admitted for therapy of a chronic duodenal ulcer of 16 years' duration. Most recent exacerbation characterized by hematemesis and melena. Blood pressure was 150/100. Skin was warm and without plethora. Neither liver nor spleen was palpable. Hemoglobin was maximum 16 gm/100 ml.; hematocrit, maximum 54%; WBC, from 8,250 to 20,900 per cubic millimeter, with normal differential; platelets, 134,000 to 260,000 per cubic millimeter. Urinalyses were normal. Other data: Total serum cholesterol was 270 mg/100 ml. (esters, 133 mg/100 ml.), alkaline phosphatase, 3.85 Bodansky units/100 ml.

CASE 7.—A 68-year-old chronic asthmatic was admitted for evaluation of coughing with dyspnea. The patient was obese, with a ruddy, almost dusky complexion. Blood pressure was 130/80. The liver was palpable, and there was bilateral pitting edema. Hematocrit was 51%; WBC, 8,250 per cubic millimeter, with a normal differential. Urinalyses were normal.

CASE 10.—A 63-year-old man was admitted for treatment of dyspnea and weakness due to idiopathic myelofibrosis with hepatosplenomegaly and myeloid metaplasia. The skin and mucosae were pallid; the liver reached the umbilicus; the spleen, the left iliac crest. Blood pressure was 160/80. Hemoglobin and hematocrit were consistently low, the maximum being 8.6 gm/100 ml. and 25%, respectively (total-body hematocrit, 34%). Reticulocytes were maximum 1.6%; platelets, 60,000 per cubic millimeter. WBC were 4,300 to 8,450 per cubic millimeter, with slight, neutrophilic granulocytosis. Bone marrow showed myelofibrosis with focal megakaryocytic hyperplasia.

Clinical Primary Hyperparathyroidism

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Introduction

The entity of primary hyperparathyroidism is relatively new. It has been only 33 years (1925) since Mandle [1] first removed a parathyroid adenoma from a patient with osteitis fibrosa generalisata and established a relationship of skeletal disease to parathyroid function. For many years hyperparathyroidism was recognized only by skeletal findings of osteitis fibrosa or von Recklinghausen's disease. It was not until 1929 that Albright, Bauer, Ropes, and Aub [2] showed that the commonest clinical manifestation of hyperparathyroidism was kidney stones.

Because of its relatively recent clinical recognition, all of the various manifestations of this disease are not always obvious. At Duke Hospital,[3] over a 25-year period, 17 cases were diagnosed in the first 24 years and 10 cases in the next 1 year.

In the past four years we have identified seven cases of hyperparathyroidism resulting from single adenomas and one with multiple adenomas, in which the presenting symptoms in seven cases were those referable to renal calculi. The symptoms, findings, and diagnosis are classical of the disease, as will be brought out in subsequent discussion. None of these eight cases had progressed to the stage where roentgenographic bone findings were present.

Comment

The most influential force affecting the concentration of calcium in the body fluids is the hormone of the parathyroid glands, and the removal of these glands is the only effective and reasonable physiologic method of rapidly lowering the serum calcium.[4] Where or how this effect is produced has been a source of controversy for a number of years.

For the past 10 years the most popular concept was that parathryoid hormone affected bone only by indirect action on phosphorous excretion. Dr. John Eager Howard [4] states that the parathyroid exerts its activity in three spheres: upon calcium metabolism, upon bone cells, and upon phosphorous metabolism. Recent experimental information indicates that parathyroid hormone affects bone directly. Proof of this has been brought out by animal experiments. Ingalls et al.[5] and Ellsworth and Futcher [6] gave parathyroid hormone to animals whose kidneys were removed, and osteitis fibrosa occurred even when the serum phosphorus was rising. Barnicot [7] and Chang [8] demonstrated that parathyroid tissue placed subperiosteally produced local osteitis fibrosa. Chambers et al.[9] demonstrated that calcium can rise without any effect on phosphorous diuresis. Phosphorous diuresis occurs soon after parathyroid hormone is administered and represents an accompaniment of the action of parathyroid hormone. The parathyroid glands are sensitive to changes in calcium concentration, responding quickly to a fall by increasing their output of hormone and to a rise by reducing their hormone production.[4]

It has been suggested by Handler and Cohn [10] that there are two or more types of parathyroid hormone: (1) the calcium-mobilizing substance responsible for dissolution of bone, hypercalcemia, and hypercalcuria and (2) the phosphaturic substance responsible for decreasing renal tubular reabsorption of phosphate, increasing urinary excretion, and lowering serum phosphorus. Munson [11] has provided data to support the above thesis also. Neuman

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et al.[12] have described a complex mechanism of action on bone whereby enzyme systems are involved with accumulation of citrate, which carries calcium from the bone as a soluble calcium citrate complex.

The kidney normally resorbs 99% of the calcium filtered at the glomerulus and is the factor permitting the serum calcium to exist at its usual supersaturated level[2]; however, when the serum calcium rises, renal excretion rises. The rise of serum calcium as the result of parathyroid hormonal stimulation is associated with its increased renal excretion.

The increased calcium excretion by the kidney may then result in the formation of calcium oxalate or phosphate stones or in the deposition of calcium salts in soft tissue of the kidney[2]; calcium may be deposited in other soft tissues in which an alkaline medium exists. Large arteries and lung and stomach tissues are those most frequently involved.

In the presence of severe renal insufficiency secondary hyperparathyroidism may occur. This is not to be confused with primary hyperparathyroidism.

Clinical Findings

The clinical findings in hyperparathyroidism can be, according to Albright et al.,[2] divided into three headings: (1) those due to bone disease, (2) those due to disease of the urinary tract, and (3) those due to hypercalcemia per se. The symptoms the patient may have are variable, and the presenting ones most commonly recognized are those relative to renal or ureteral calculi. Several authors have commented on the long time many patients have had their symptoms.[2,3] One of our patients had known symptoms of renal calculi for at least 25 years, and another, for 10 years.

Hellström[13] reported that 60% of the patients with hyperparathyroidism reported in the literature had renal calculi and only 25% have had osteitis fibrosa generalisata. Goldman[14] and Black et al.[15] give similar figures. Many patients with renal findings will not have any evidences of skeletal change. It has been stated by Albright et al.[2] that there must be a loss of at least 30% in all mineral content of bone before significant changes in the density of bone become recognizable by roentgenography.

Findings related to the urinary tract may be divided into simple hyperphosphaturia and hypercalcemia, renal calculi, or deposition of calcium in renal parenchyma. Seven of the eight cases in our series had only renal calculi, and the eighth had not only renal calculi but also renal calcinosis. Renal calculi that occur may involve one or both kidneys and may keep recurring as long as parathyroid gland hyperfunction exists. In all except one of our cases, renal calculi had been present bilaterally at some time and had produced the chief symptoms for which the patient sought aid. Secondary infection of the kidney is frequently present.[2,16] Two of our patients had had renal infection for years. Repeated operations for calculi have been a common part of the history, and as the condition continues the kidneys are damaged by stones and infection and/or deposition of calcium in kidney substance. Milne[17] has stated that 1.3% of the patients with renal calculi have hyperparathyroidism.

There had been eight operations for renal calculi in the series here reported, and, of these eight, two were nephrectomies because of severe renal damage. Two patients had had renal calculi removed and had them re-form, to be removed a second time.

Other, less common, symptoms that are frequently present are listed by Bogdonoff et al.[3]: lassitude, muscle weakness, weight loss, bone pain, bradycardia, cardiac irregularities, leg ulcers, peripheral vascular disease, band keratitis, nausea, vomiting, polyuria, polydipsia, constipation, and muscle pain. This admixture of symptoms is not necessarily characteristic of any one disease and frequently leads to a diagnosis of psychoneurosis. Many of these symptoms

were common to our group, as noted in the following list:

Renal calculi	8
Constipation	4
Nervousness	4
Polyuria	4
Lethargy	3
Pyuria	2
Muscle pains	2
Weight loss	2
Renal calcinosis	1

In one instance the presenting symptom was severe constipation. Psychotic symptoms have also been noted, by Fitz [18] and by Bogdonoff et al.,[3] to be the presenting symptoms, with manifestations such as delusions, general stupor, impairment of memory, or psychic fatigue. Gutman,[19] Rogers,[20] and others [2] noted also that a great many patients have symptoms of a duodenal ulcer which may be demonstrated by roentgenography. Gastrointestinal symptoms may be the presenting complaint. Cope et al.[22] have commented on the possible relationship of acute pancreatitis and hyperparathyroidism. Four of our eight patients had gastrointestinal symptoms, and four had proven duodenal ulcers. Hypomotility of the bowel leads to severe constipation in many patients, and a slowly progressive rising blood pressure may be noted in others. Three out of eight in our series had diastolic blood pressure above 90 mm. of mercury.

Extensive vascular calcification with clinical evidence of arterial insufficiency had been noted by several others, including Rogers,[20] Albright,[2] Ellis and Barr,[23] and Bogdonoff et al.[3] Rogers [20] describes areas of necrosis and intimal calcification in the walls of almost all larger arteries, found at postmortem examination of a patient who had parathyroid gland hyperplasia. Bogdonoff et al.[3] reported finding extensive calcification of small arteries and arterioles, involving intima and/or entire vessel wall and in larger vessels producing characteristic changes of Mönckeberg's sclerosis.

Several authors [14,21] have reported the presence of other endocrine gland disturbances in patients with parathyroid adenomas. The presence of pituitary tumor and pancreatic islet-cell tumor with parathyroid hyperfunction has been noted.[2,24-26] Hyperthyroidism and hyperparathyroidism have been reported, by Hellström [24] and Pribek et al.,[27] as occurring together. Also, hyperparathyroidism and adrenal hyperplasia have been noted [28] occurring together. Three of our eight patients had nonfunctioning thyroid adenomas at one time or another.

Multiple systems involvement may occur to such an extent as to suggest a diffuse collagen disease.[3]

Diagnosis

The diagnosis of this disease depends first upon a suspicion of the existence of such a condition. By all means, all patients with renal calculi should have an investigation for possible parathyroid hyperfunction. Hypercalcemia and hypophosphatemia are the most important diagnostic clues to hyperparathyroidism. Whenever the blood calcium rises above the levels of 11 mg. % and the phosphorus is less than 3 mg. % one must be suspicious of hyperparathyroidism. Some authors [2,3] have stated that such findings are almost diagnostic of hyperparathyroidism. A patient may have a normal serum calcium and a low phosphorous, or vice versa, in the presence of this disease. Bogdonoff et al.[3] place greater emphasis on a hypophosphatemia with normal calcium than on an elevated serum calcium with normal phosphorus, while Chambers and his group [9] believe that an elevated serum calcium is of more significance than the low phosphorus when both values are not abnormal at the same time.

In our 8 cases there were 31 determinations for calcium and phosphorus prior to surgery. The serum calcium was above 11 mg. % and the serum phosphorus below 3 mg. % in all except three instances, and in two of these instances they were in related blood samples. The highest serum calcium value was 15.3 mg. % and the lowest 10 mg. %, with an average of 12.8 mg. %. The highest phosphorous value recorded was 3.1 mg. % and the lowest 1.8 mg. %,

with an average of 2.43 mg. %. None of these patients was subjected to stress tests. In all instances the diagnosis was verified at surgery.

These patients frequently have increased Sulkowitch test results, demonstrating abnormal amounts of calcium excretion in the urine. We found abnormal Sulkowitch test results in four of our eight patients.

The elevated serum calcium and low phosphorus, combined with evidences of renal calculi or other roentgenographic findings, such as subperiosteal bone absorption in the hands, bone cysts, the absence of the dental lamina dura, or other abnormal soft tissue calcifications, are justification for surgical exploration for a parathyroid tumor.[29] Other diagnostic procedures which can be performed when doubt still exists as to the diagnosis are tests for the tubular reabsorption of phosphate, for calcium tolerance, and for phosphate deprivation.[9,30] One must remember in the evaluation of laboratory procedures that a lowered serum calcium can lead to erroneous conclusions. The electrocardiogram occasionally may suggest the diagnosis of hyperparathyroidism by a short Q-T-interval and almost absent ST-segment.[31] None of our series had an abnormal electrocardiogram.

A differential diagnosis of hyperparathyroidism would include such conditions as multiple myeloma, hypervitaminosis D, Paget's disease, sarcoidosis, osseous metastasis or renal disease with secondary hyperparathyroidism, and the milk alkali syndrome. This latter condition can be extremely difficult to differentiate from hyperparathyroidism, and it is the opinion of Black [21] that it cannot be differentiated with complete certainty in patients with primary hyperparathyroidism who have some degree of secondary renal insufficiency.

Pathology

Albright [2] states that primary hyperparathyroidism is an overfunction of the parathyroid glands as the result of either a single parathyroid adenoma, multiple adenomas, hypertrophy of all parathyroid tissue, or a carcinoma of one gland. The chief significance of hyperparathyroidism is the irreversible damage produced to various tissues of the body if the condition is permitted to continue, and Hellström [13] particularly has stressed the irreversible renal lesions that may occur. There is no problem in recognizing hyperparathyroidism once the patient has developed symptoms characteristic of osteitis fibrosa generalisata. With our present knowledge of the disease, very few patients should ever reach this late stage.

Black and Zimmer,[15] in reviewing 207 cases of hyperparathyroidism, found 86% of the patients had a single adenoma, consisting of small or large chief cells with additional water-clear cells, also called wasserhelle cells. Six per cent of the patients had multiple adenomas, and seven per cent represented primary hyperplasia in which all glands are involved with the so-called water-clear type cell. Less than 1% had a functioning carcinoma. Seven of our eight patients reported here had single primary parathyroid adenomas, and one had multiple adenomas.

Treatment

Once a diagnosis of hyperparathyroidism is made, a surgeon is committed to find and remove all the excess hyperfunctioning tissue. If the excess parathyroid tissue is not found in the usual location near the thyroid gland, the surgeon must expose the posterior mediastinum and even the anterior mediastinum. There may be confusion with a thyroid adenoma or even lymph node enlargement. The operation should not be undertaken by a surgeon who has not made a study of the appearance and location of normal glands. Occasionally roentgenograms of the neck prior to surgery will reveal the location of a parathyroid adenoma [32]; occasionally parathyroid adenomas are of such size that they can be felt prior to operation. It is not proposed to enter into a discussion of the surgical technique involved but to refer you to surgical discussion on the subject.

Postoperative Cautions

One must be aware that when a parathyroid adenoma is removed the patient may experience hypocalcemia following surgery. This is particularly true when there has been loss of calcium from the bone in very large quantities. Once the excess parathyroid stimulus has been removed, the calcium is rapidly deposited in bones again. The deposition may be at such a rate that serum calcium is lowered to abnormally low levels, with the result that tetany occurs. It may be necessary to give the patient intravenous calcium or even dihydrotachysterol (Hytakerol) for a few days or weeks following surgery. When there is no roentgen evidence of bone changes prior to surgery or the alkaline phosphatase is below 33 mg. %, there is much less likelihood of hypocalcemia after removal of an abnormally functioning gland.

Summary

A discussion of the physiology, symptoms, and diagnosis, with brief mention of pathology and treatment, of primary hyperparathyroidism is given, with special emphasis on renal calculi. Included in this discussion is the presentation of the findings in eight cases of hyperparathyroidism identified in clinical practice in the past five years.

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Saluretic and Toxic Effects of Amphenone in a Patient with Cirrhosis and Ascites

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The precise pathogenesis of ascites in cirrhosis of the liver remains obscure. Portal hypertension,[1,2] decreased plasma osmotic pressure due to hypoalbuminemia,[3,4] increased lymphatic exudation from the liver,[5,6] increase of antidiuretic hormone,[7] and increase of sodium-retaining adrenocortical hormone[8] are among the factors considered in the pathogenesis of ascites. The marked decrease of sodium excretion and the presence of increased amounts of aldosterone in the urine of patients with cirrhosis and ascites[9] point to this sodium-retaining hormone as the possible culprit in the pathogenesis of ascites. The complexity of the pathogenesis of ascites is demonstrated schematically in Figure 1.

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The Amphenone used in this investigation was obtained from Dr. C. H. Sullivan of Ciba Pharmaceutical Products, Inc., Summit, N. J.

Attending Physician in Medicine, Michael Reese Hospital, and Associate Professor of Clinical Medicine, University of Illinois College of Medicine, Chicago (Dr. Spellberg); Resident in Medicine, Michael Reese Hospital (Dr. Chaikoff).

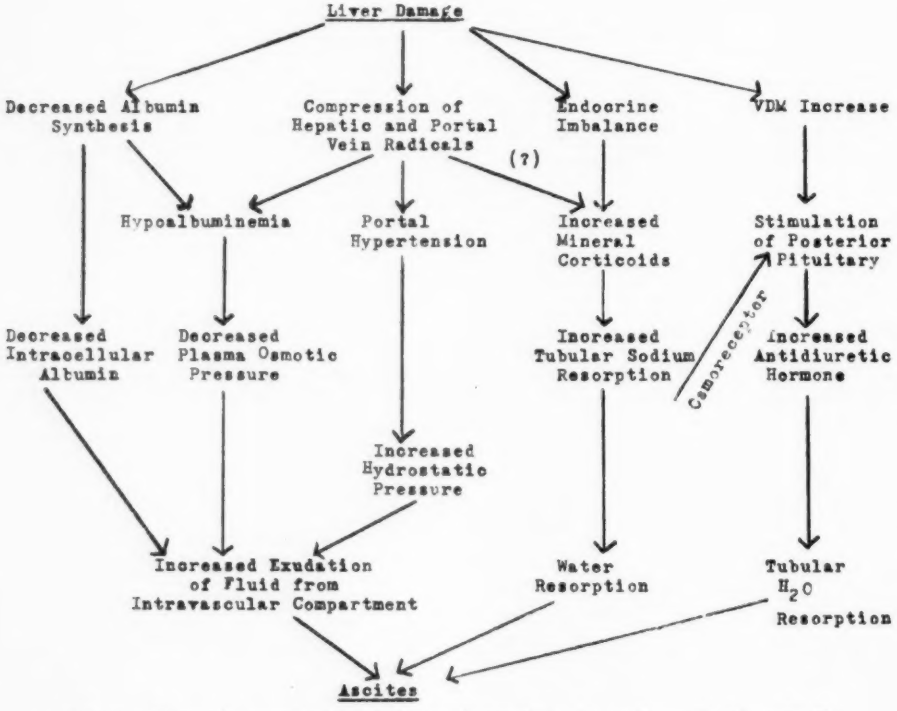

Fig. 1.—Schematic presentation of factors involved in the pathogenesis of ascites.[10]

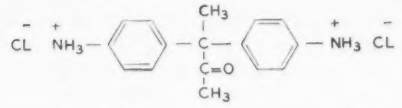

Fig. 2.—Formula of Amphenone B.[25]

Amphenone B (3,3-bis[*p*-dimethylaminophenyl]butanone-2-dihydrochloride) (Fig. 2) was synthesized by Allen and Curwin,[11] in 1950, and has been shown to have principally an inhibiting effect on thyroid and adrenocortical function.[12,13] Among its other effects are a progesterone- or estrogen-like effect on the female genitalia, with uterine enlargement [12] and a depressing effect on the central nervous system.[12] Surgical anesthesia has been produced in animals with large doses of intravenous Amphenone.[14] The goitrogenic effect is similar to that produced by other antithyroid drugs. The adrenocortical effect consists of an inhibition of synthesis of adrenal hydroxycorticoids and aldosterone with a concomitant enlargement of the adrenal cortex owing to accumulation of lipids in the cells of the zona fasciculata and reticularis. The hypertrophy of the adrenal cortex does not occur in the absence of pituitary corticotropin. The inhibition of aldosterone synthesis is the basis for its use in the treatment of ascites.

Report of a Case

This 31-year-old woman with postnecrotic cirrhosis had had nine admissions to the hospital in the last two years, for the treatment of hepatic coma, precoma, and ascites, and in January, 1957, for dilation and curettage for persistent menorrhagia. The episodes of coma responded to steroids,[17] and the ascites was previously treated with paracentesis, intravenous albumin, and diuretics. In May, 1957, ascites was successfully treated with sodium restriction and chlorothiazide (Diuril).* In July, 1957, she was treated for ascites by paracentesis and intravenous albumin. She was maintained on chlorothiazide (1 gm. daily) and remained free of ascites and edema in spite of increased sodium intake until 10 days before admission, on Sept. 26, 1957. Rapid weight gain (15 lb. in 10 days) and abdominal enlargement necessitated readmission to the hospital.

In spite of sodium restriction of 200 mg. per day and bed rest, weight gain continued and ascites increased (Table 1). Urinary sodium output was 10.8 mg. (0.4 mEq.) and 12.3 mg. (0.53 mEq.) per 24 hours. The patient was placed on 10 mg. of prednisone thrice daily prior to the administration of Amphenone.[19] The urinary sodium excretion decreased to 1.6 mg. (0.07 mEq.) per day.

On Oct. 8, the patient was started on 3 gm. of Amphenone daily in divided doses. Two days later the Amphenone was increased to 6 gm. per day

* The chlorothiazide used was donated by Merck Sharp & Dohme, Division of Merck & Co., Inc., Philadelphia.

TABLE 1.—*Treatment Data*

Date	Weight, Lb.	24-Hr. Urine, Cc.	24-Hr. Urine Sodium	Amphenone & Prednisone	Paracentesis Vol., Cc.
9/30	133	960			
10/1	134				
10/2	134 ½	820	10.8 mg. (0.47 mEq)		
10/3	134 ¾	740	12.3 mg. (0.53 mEq)	Prednisone started	
10/4	135	690			
10/6	137 ½	900			
10/7	140		1.6 mg. (0.07 mEq)		
10/8	140 ½	620		Amphenone started	
10/9	143	480			
10/10		900			
10/11		740	9.5 gm. (413 mEq)		
10/12	145	840		Amphenone discontinued	
10/13	148	600			700
10/14	130	960			6,420
10/15	120	2,520			900
10/16	118	1,500			
10/17		3,100	7.8 gm. (339 mEq)		
10/18		3,450			
10/19		2,220			

TABLE 2.—*Liver-Function Tests* *

Date	Total Protein, Gm.	A/G	Bilirubin, Mg.	Cholesterol Esters	TT Units	TF	CCF	Prot. Time, Sec.	Alk. Phosph., Units	Glutamic Transaminase
9/27	6.6	1.8:4.8	5.2	163/50	10	1+		20	10.3	95
10/3	6.1	2.2:3.9	6.0						10.4	
10/7	6.0	2.0:4.0	4.6	143/86	8.2	2+	3+	18.2		44
10/12	6.2	2.1:4.1	3.6	149/89	6.1	1+	2+	18.4	11.5	
10/15	7.0	2.4:4.6	3.9	216/130	7.4	2+	3+			
10/22	5.3	1.7:3.6		185/120			3+	24.2		
10/25	5.8	1.6:4.2	13.6	123/55	5.4		3+			94
10/26	Died									

* TT indicates thymol turbidity; TF, thymol flocculation; CCF, cephalin-cholesterol flocculation.

because diuresis did not occur and the ascites continued to increase.

Amphenone in 6 gm. daily doses was continued for two more days, but diuresis did not occur and the ascites did not decrease, this in spite of a sharp rise in sodium excretion to 9.5 gm. (413 mEq.) on the third day of Amphenone administration. Amphenone was stopped on the fourth day because of its apparent ineffectiveness in reducing the ascites and because of marked lethargy.

The patient had had several episodes of coma and precoma previously and several days after entering the hospital showed marked changes in mood. Atypical flapping tremor of the hands was noted Sept. 28. Lethargy also developed, which seemed to subside somewhat on prednisone therapy. The flapping tremor likewise disappeared. When Amphenone was started the patient became much more lethargic, the speech became slowed, and the patient complained of blurring of vision and acted and talked like a person intoxicated with alcohol. She likened her state of consciousness to one inebriated. Marked coarse tremor of hands developed, but the flapping tremor did not reappear. On the third day of therapy pronounced vertical nystagmus developed and tendon hyperreflexia developed. Anorexia, which was present before, became more marked, and with the lethargy no food was ingested. The Amphenone was discontinued on the evening of the fourth day of therapy, and two days later a paracentesis was done, with a polyethylene tube left in situ for 48 hours.

Total ascitic fluid removed was 8,020 cc. Forty-eight hours after the polyethylene tube was placed in the peritoneal cavity and about seventy-two hours after discontinuance of Amphenone marked diuresis occurred. The patient lost 30 lb. in weight in three days, and at this point lethargy, which had briefly disappeared, returned; ankle clonus developed, and the patient went into deep coma and died Oct. 26, thirteen days after paracentesis.

The treatment of hepatic coma consisted of intravenous hydrocortisone, up to 300 mg. daily; sodium glutamate intravenously, 20-40 gm. per day; 10% dextrose, ascorbic acid, vitamins of the B-complex series, tetracycline intravenously and/or intragastrically, and electrolytes as needed.[17]

The laboratory data are tabulated in Tables 2 and 3. There was a marked rise in serum bilirubin and further fall of the serum albumin, an increase in prothrombin time, and a fall of free and esterified cholesterol.

The serum sodium decreased during Amphenone therapy. The potassium remained normal but rose preterminally. The CO_2 rose, probably from sodium glutamate therapy. The blood urea nitrogen likewise increased preterminally.

TABLE 3.—*Blood Chemistry*

	Blood Chemistry								
Date	FBS, Mg. %	BUN, Mg. %	Creatinine, Mg. %	Na, mEq/L.	K, mEq/L.	Cl, mEq/L.	CO_2, Mm/L.	Ca, g. M%	P, Mg. %
9/27	48	11.5	0.6	141	3.7	104	24.0	9.8	
10/3				136	3.9				
10/12				128	5.2		22.9		
10/15				128	4.0	95.5	29.7		
10/22		33.5		131	4.5	87	35.8	12.3	2.7
10/25		69.5		139	6.7	104	30.3	11.4	4.3
10/26	Died								

Autopsy† revealed the following pertinent findings. The liver weighed 700 gm. and revealed both coarse and fine nodules. The histologic picture was compatible with postnecrotic cirrhosis. There was a recent thrombosis of the portal vein. Esophageal varices were present, but no ulcerations, erosions, or hemorrhage were noted.

The pancreas was enlarged to 130 gm. and showed recent focal fat necrosis, as well as chronic interstitial pancreatitis. The kidneys were markedly enlarged, weighing 410 gm. The gross and histologic changes were those of cholemic nephrosis.

The thyroid gland was of normal size. Microscopically it revealed increased amounts of interstitial connective tissue. In many areas the follicles were dilated and lined with one layer of swollen tall cuboidal epithelial cells with relatively small, dark-stained nuclei and granular acidophilic cytoplasm, resembling the Hurthle cells. Some of these cells contained unusually large nuclei. Some areas showed hyperplasia of the cells of the follicles. Such changes are seen in thyroids of animals treated with Amphenone. In other areas the follicles were shrunken, and the cells were undergoing regressive changes. The stroma was infiltrated by lymphocytes and other mononuclear cells.

The adrenal glands were of normal size and showed no increase of intracellular fat or other structural abnormality.

Comment

The effective and rational therapy of ascites in liver disease depends on our ability to normalize the altered physiology which is responsible for this complication. The incrimination of sodium-retaining hormones of the adrenal gland and especially aldosterone is logical, especially since an increase of aldosterone has been noted in patients with cirrhosis and ascites.[9] A chemical substance for inhibition of adrenal sodium-retaining steroids seems more rational than bilateral adrenalectomy, which has been attempted for the treatment of intractable ascites.[18]

The inhibition of aldosterone secretion and sodium diuresis has been demonstrated by Thorn, Renold, and their co-workers.[19,20] Wolfe[21] and co-workers have demonstrated sodium diuresis in four patients with cirrhosis and ascites. It is noteworthy that no marked water diuresis had occurred in the patients reported in the literature[19-21] or in our patient. There is no satisfactory explanation for this. A marked rise in sodium excretion was noted in our patient from virtually none (10-12 mg., or 0.4-0.5 mEq.) to over 9 gm. (413 mEq.) on the fourth day of Amphenone therapy. Marked water diuresis occurred 48 hours after paracentesis and 4 days after discontinuance of the Amphenone. This could have been a sign of delayed action of the Amphenone in mobilizing excretion of water, but more likely the diuresis was a response to the paracentesis.

The slight or absent water diuresis, as compared with sodium diuresis, is disappointing, because it impairs the usefulness of Amphenone as a therapeutic agent for ascites of hepatic orgin. It also casts doubt upon the theory that the water retention in liver disease is dependent on the increased activity of sodium-retaining steroids and may favor the theory of an increase of antidiuretic hormone of posterior pituitary origin.

A most serious drawback to the use of Amphenone clinically is its effect on the central nervous system. The drowsiness simulated hepatic coma; however the patient remained clear mentally and showed no confusion, as is the case of hepatic coma or precoma. The sensorium effect and gait resembled early alcoholic intoxication. There was also mild euphoria and slurring of speech. Coarse tremor of fingers developed, and pronounced vertical nystagmus may have been due to the effect of Amphenone on the nervous system, although one cannot exclude hepatic encephalopathy as their cause. Dermatitis, gastrointestinal symptoms, and methemoglobinemia have been observed during prolonged administration of Amphenone.[13] The development of true hepatic coma cannot be related to the Amphenone but may have been precipitated by paracentesis.

There was no morphologic evidence that the Amphenone precipitated the downhill

† Autopsy was done by the Department of Pathology of Michael Reese Hospital, Dr. Otto Saphir, Director.

course. The portal vein thrombosis, the focal fat necrosis of pancreas, and the interstitial pancreatitis are not infrequent complications of advanced cirrhosis.

We were particularly interested in the effect of Amphenone on the adrenal glands, the uterus, the thyroid, and the brain. The first three have shown changes in animals treated with Amphenone. The enlargement of the adrenal cortex noted in animals was not present in our patient, whose adrenal glands were histologically normal. The enlargement of the adrenal cortex in the experimental animal appears to be due to the stimulating effect of corticotropin (ACTH), but in our patient the pituitary effect was inhibited by prednisone administration.

The uterine enlargement reported in animals was not found in our patient. A goitrogenic effect has been noted in animals. Although our patient showed no thyroid enlargement, there were histologic changes indicative of a subacute thyroiditis and hyperplasia of the epithelium of the thyroid. It may be postulated that the Amphenone affected some of the histologic changes in the thyroid.

There were no structural abnormalities in the brain that could be attributed directly to Amphenone. There were a few areas in the cerebral cortex which showed an increase of neuroglia cells. This finding is seen in patients dying in hepatic coma.

It is evident from our experience in this patient, as well as from the experience of others, that Amphenone is not an ideal therapeutic agent for the treatment of ascites because of its marked side-effects and its tendency to produce good sodium diuresis but poor water diuresis. Perhaps modifications of Amphenone or other substances which inhibit the adrenal cortex or antagonize aldosterone may be more useful clinically. Thus chlorethane (Perthane) (2,2-bis-[*p*-ethylphenyl]-1,1-dichlorethane), an insecticide structurally related to D. D. T., has been noted to depress adrenocortical activity.[22] Likewise, a steroidal antagonist of aldosterone has been synthesized which has a saluretic effect.[23,24] Perhaps the effective treatment of ascites in cirrhosis will emerge from one of these newer compounds.

Summary and Conclusions

Amphenone (3,3-bis[*p*-dimethylaminophenyl]butanone-2-dihydrochloride) was administered to a patient with ascites and postnecrotic cirrhosis. A marked increase in sodium excretion was noted on the third day, but urine volume did not increase at that time. Amphenone was discontinued on the fourth day, and paracentesis was resorted to. Marked increase of sodium and water excretion took place after paracentesis, but the patient went into hepatic coma and died.

The only morphological effects attributable to the Amphenone observed post mortem were hyperplastic changes in the thyroid gland. The rationale and deficiences of Amphenone therapy are discussed. It is suggested that perhaps factors other than aldosterone may have been more important in the etiology of ascites in this case.

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Caval Contrast Radiography

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Roentgen visualization of the inferior vena cava has been found advantageous in many instances, since abnormalities of the venous circulation of the trunk and lower extremities are usually discovered late in the history of a patient's disease and even then are often poorly understood. A common basis for these pathological changes lies in partial or complete occlusion of the vena cava. Primary caval occlusion, as by intrinsic tumor or effort thrombus, is an extremely rare disease. The proximal cause of caval disease, whether metastatic tumor, growing thrombi, or benign compression, may not be suspected without such additional clues as may be furnished by visualizing the inferior vena cava roentgenologically.

Indications and Contraindications

The occasion frequently arises when the urologist, the internist, or the general surgeon needs to know more about the condition of the inferior vena cava and the immediately adjacent areas and when, in many such cases, surgical exploration is not justifiable. It is in this sort of problem that the information given by a "cavagram" is most helpful. The limitations of surgical treatment may be predicted when neighboring neoplasms invade or occlude the inferior vena cava. Inflammatory adhesions of the inferior vena cava may make surgery more hazardous, and a foreknowledge of these difficulties may be of aid to the surgeons. The chances of survival of the patients who have carcinoma of the kidney are seriously curtailed by extension through the renal veins into the vena cava, and this information may be valuable to the urological surgeon in his management of the patient with this disease. The aorta is also closely adherent to the vena cava, and if an aneurysm of the abdominal aorta is wrapped with cellophane the cava may be easily damaged unless the existence of adhesions and deflections is appreciated. Tumors of the pancreatic head, which are notoriously difficult to diagnose, may reveal their presence and their extent by their compression of the vena cava rather than by enlargement of the loop of the duodenum. The anomalous persistent postcardinal vein, which results in a retrocaval ureter, may be demonstrated with this method. Hepatic enlargement, often due to intrahepatic masses, may cause a nonspecific compression of the cava, and this may be one of the few signs of hepatic abscess. Since the preparation, the contrast media, and the indications are much the same as for intravenous urography, one may accept the indications for urographic examination as adequate for roentgen visualization of the inferior vena cava in addition to the specific indications partially enumerated.

When there is a clinical indication for the use of this method, no absolute contraindications are known to exist. Sensitivity tests help to rule out any idiosyncracy to iodopyracet (Diodrast), and, since ionizable iodine is not ingested, iodism need not be feared. Extravascular injections are troublesome but, like other technical difficulties, are infrequent when more experience in femoral venipuncture is acquired. The need for development of a reliable roentgen technique for caval visualization was realized by dos Santos, in 1935, and later, but separately and independently, by Castellanos et al., Farinas, and ourselves.

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From the Minneapolis Veterans Administration Hospital.

Technique

The diverse techniques thus developed offer an interesting contrast. Each one has advantages and disadvantages that limit its application. In the method proposed by Castellanos et al., the femoral vein is surgically cannulated at the ankle, while Farinas advises saphenous surgical cannulation. Both recommend use of 50% to 75% iodopyracet as a contrast medium. They have successfully demonstrated the vena cava with such methods.

To perform this examination, one prepares the patient as for an intravenous urogram. When the scout film shows the patient's abdomen to be suitably free of gas and opaque material to allow caval visualization, the skin of the patient, who is lying supine on the x-ray examination table, is prepared for aseptic venipuncture after palpation and localization of the femoral artery on the side to be examined. A procaine hydrochloride (Novocain) wheal is raised 5 mm. medial to the femoral artery 4 cm. below Poupart's ligament. The femoral vein is then punctured just medial to the femoral artery and under the site anesthetized, with a 19-gauge needle on a 30 cc. syringe of 35% iodopyracet. After enough venous blood is withdrawn to assure a good tap, the iodopyracet is injected with moderate rapidity into the vein. A speed of 1 cc. per second is adequate. At the end of the injection, the x-ray exposure is made. The patient is then rolled into a lateral position and the injection repeated to obtain the lateral view. It has been found that a small segment of rubber tubing between the needle and the syringe allows this maneuver without displacement of the needle from the vein.

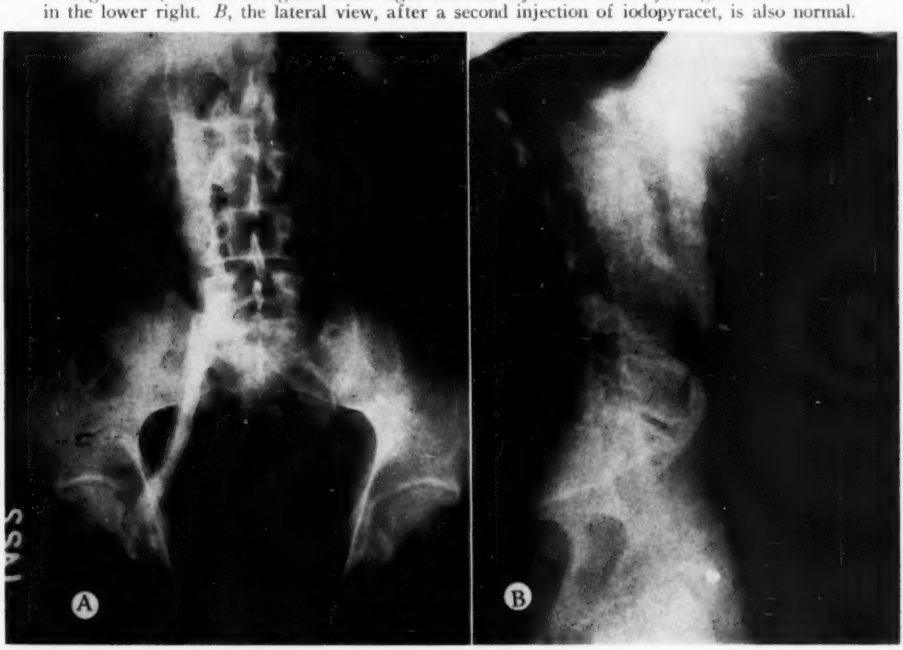
Using this technique with a lower concentration of the organic iodinated media injected close to the point of interest, we have found results comparable to those found with more highly concentrated media. Spasm, phlebothrombosis, and anaphylaxis, often seen with the more concentrated compounds, are largely absent. The percutaneous rather than surgical approach makes the method more widely utilizable and less inconvenient to the patient and to the operator and minimizes morbidity. We feel that these factors make this a practical method of visualization of the inferior vena cava and one which is easily adapted to general use.

Comment

In addition to the demonstration of the normal vena cava and a determination of its normal variations, we have demonstrated many of the pathologic entities discussed as indications for the examination.

Venous tributaries are shown in patients who have an increase in abdominal venous

Fig. 1.—*A*, normal cavagram after right femoral injection. The injecting needle is visible in the lower right. *B*, the lateral view, after a second injection of iodopyracet, is also normal.



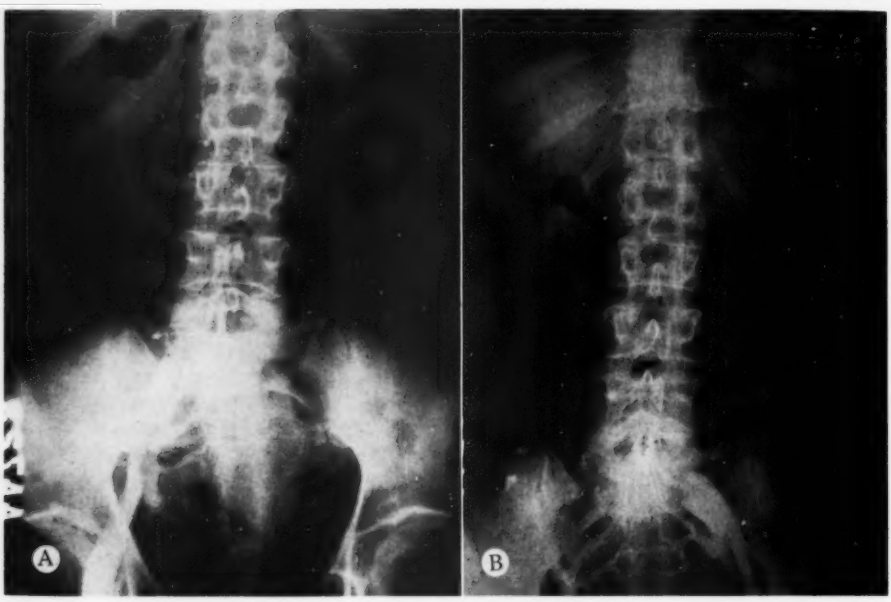


Fig. 2.—*A*, occlusion of the cava is present with good visualization of the sacral, vertebral, and thecal venous plexuses. No signs of caval disease are present save for meralgia paraesthetica. *B*, the same patient, injection being on the left. Note the excellent visualization of the meningorachidian veins.

Fig. 3.—*A*, high partial caval occlusion in a patient with pulmonary carcinoma. The azygos vein arises at the level of the renal vein and ascends medial to the cava and is continuous with the ileolumbar veins. *B*, lateral view of the same patient, showing the same veins in another projection.

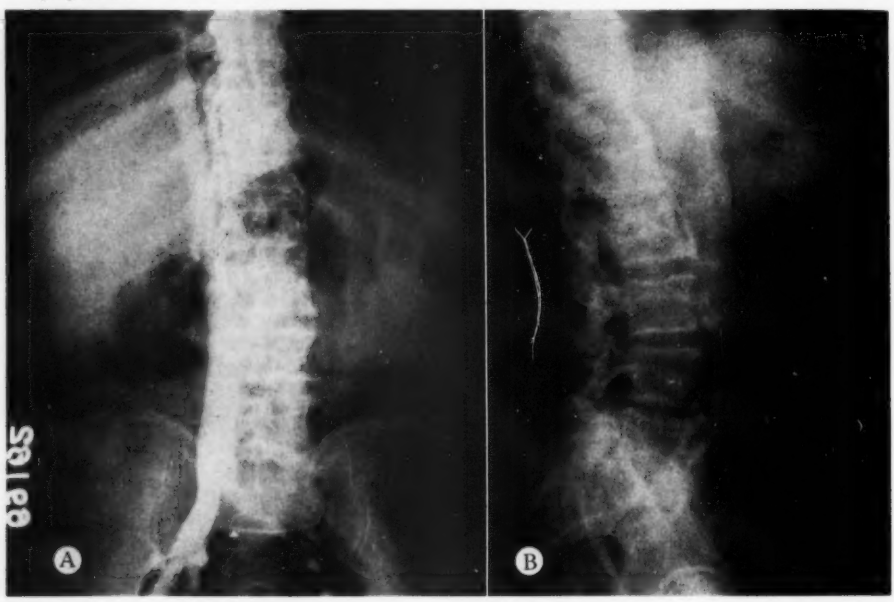


Fig. 4.—Valsalva maneuver with the normal cava opacified with 35% iodopyracet. Note the valves of the tributary veins which normally prevent reverse flow into the vertebral plexus.

Fig. 5.—The cava is adherent to and is deflected by a large aortic aneurysm. The cava was torn upon attempted "wrapping" of the aneurysm.

pressure due to a partial back-flow. Using the Valsalva experiment, we have shown the competence of the valves at their orifices. Only in patients with long-standing significant caval occlusion can we fill the vertebral plexuses. This may not be entirely in keeping with Batson's theory of retrograde metastatic tumor spread from the pelvis, but such findings cast some doubt on the universality of application of this theory. The vertebral plexuses in the living human have been demonstrated by means of this method. The integrity of the caval tributaries may be maintained, and this too has been shown from the contributions graphically. Effort thrombosis and malignant thrombosis of the vena cava, as well as two interesting corollary phenomena in this type of disease, have been discovered in this way. Electrocardiographic abnormalities of the L-T segment were frequently found with caval occlusion. Another incidental observation was a renal appearance, similar to that seen in polycystic kidney, due, it is thought, to renal venous congestion and edema.

Conclusions

The technique for contrast roentgen visualization of the inferior vena cava of the living human is presented. Clinically significant observations are offered to support the claims for the value of the procedure. No absolute contraindications to the examination are known.

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Serum Cyanocobalamin (Vitamin B_{12}) as an Index of Hepatic Damage in Chronic Congestive Heart Failure

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It has been shown that liver-cell damage caused by various agents (viral,[1-4] chemical,[5] infiltrating tumor [6]) is associated with markedly increased levels of cyanocobalamin (vitamin B_{12}) in the blood, which are due to the release of the vitamin from damaged liver cells.

This report deals with observations on cyanocobalamin activity in the serum of patients with severe congestive heart failure associated with hepatomegaly.

Material and Methods

Twenty-eight patients suffering from chronic congestive heart failure due to arteriosclerotic, rheumatic, or congenital heart disease were studied. In all patients marked hepatomegaly was present as well as venous engorgement; in some there was also ascites and peripheral edema. The duration of right heart failure preceding the time of the present examination varied from several months to seven years. Cyanocobalamin was determined mircobiologically with a mutant strain of Escherichia coli, as described previously.[7,8] In some cases, repeated cyanocobalamin determinations were made before and after treatment for congestive heart failure. In addition to cyanocobalamin determinations, the commonly used liver-function tests were performed.

Results

As seen in the Table, in patients with congestive heart failure, the cyanocobalamin values ranged from 500$\mu\mu$g. to 3,500$\mu\mu$g. per milliliter, while the serum cyanocobalamin levels in normal persons fall in the 200$\mu\mu$g. to 500$\mu\mu$g. per milliliter range. In 23 of 28 patients studied, elevated serum cyanocobalamin concentrations were found; among these, in 11 there were values of 1,000$\mu\mu$g. per milliliter or above. Of the five patients with normal cyanocobalamin levels, three (Cases 21, 26, 27) had congestive failure of recent onset. The fourth patient (Case 23) was suffering from constrictive pericarditis with marked ascites and hepatomegaly of seven years' duration. The last (Case 22, 14 years old) was suffering from congenital heart disease with marked cyanosis. In eight patients in which repeated cyanocobalamin estimations were performed, a decrease in the vitamin level occurred which coincided with the amelioration of the congestive failure. This was illustrated in Case 19, who was suffering from chronic congestive heart failure due to mitral stenosis and insufficiency (Fig. 1). The first clinical signs of right heart failure and hepatic congestion appeared three years preceding admission. At the time of examination he was in a state of severe congestive failure with generalized anasarca. The liver was markedly enlarged, the lower border extending 10 cm. below the right costal margin. The venous pressure was 250 mm. of saline. The cyanocobalamin in the serum shortly after admission was 3,500$\mu\mu$g. per milliliter. After treatment, diuresis resulted in a 6 kg. weight loss and the liver decreased in size considerably. The serum cyanocobalamin concentration, though still elevated (1,500$\mu\mu$g. per milliliter), was definitely lower than before. Subsequent serum cyanocobalamin values showed a further decline, up to 920$\mu\mu$g. per milliliter. When the lowest cyanocobalamin concentration was obtained, the liver was still enlarged and firm.

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TABLE 1.—*Serum Cyanocobalamin Levels and Liver-Function Test Results in Patients with Congestive Heart Failure*

Patient No.	Date (1957)	Serum B_{12}, μμg/Ml.	Billrubin, Mg. %	Ceph. Floc.	Thymol Turb.	Alk. Phosph.	Cholesterol, Mg. %	A/G	Diagnosis *
1	July 4	835	0.7		2.7	4.9	144	3.5:3.3	CHD
	July 15	900	1.6	++	3.0	7.9	155	4.2:3.5	
2	July 3	2,500	1.2	++	1.9	6.6	174	3.6:3.0	RHD
	July 12	1,800	1.6	+	2.2	8.8		3.3:3.3	
	Sept. 16	1,790	2.6	++	2.0	8.4	161	3.8:2.8	
	Oct. 23	2,000							
3	June 26	1,010	0.2	+	0.9	2.7	414	3.8:2.3	AHD
4	May 12	2,500	1.2	—	1.2	5.2	253	3.2:2.0	AHD
	June 9	2,000	1.0	—	0.6	5.7		3.2:2.5	
	Aug. 14	1,080		—	3.5	10.6		3.2:2.5	
	Nov. 8	970	1.0	++	2.5		240	3.3:2.6	
	Nov. 13	675							
5	July 10	480							
	July 26	760		—	1.2		128	3.2:2.4	RHD
	Aug. 4	1,130							
6	Aug. 16	700	1.8	+	3.8	5.0		3.3:3.1	AHD
	Sept. 23	900							
7	Aug. 29	600							AHD
8	Aug. 26	1,000	1.0	—	1.7	5.4		3.0:2.3	RHD
9	July 26	1,500					110	3.0:2.6	AHD
	July 31	1,220	1.8	—	1.7	9.6	149	3.6:3.1	
10	Aug. 4	840	2.4	—	1.8	6.7	171	3.6:2.9	AHD
11	Aug. 2	1,100	0.6	+++	5.7	5.3	183	3.8:4.6	RHD
	Oct. 5	700	0.4	++	3.0	4.5	153	4.2:3.9	
12	Aug. 1	1,000				2.1	102	3.9:4.5	AHD
13	Jan. 20	950	3.6	++	4.3			3.5:2.0	RHD
14	Oct. 7	1,500	2.3	+	6.3		171	3.2:4.0	AHD
15	Nov. 3	770						4.1:3.0	RHD
	Nov. 13	700	1.8	—	3.3	4.5	163		
16	Nov. 14	900						3.9:3.3	RHD
	Nov. 22	470							
17	July 9	670	0.7					3.0:5.0	AHD
	Nov. 11	380							
18	Dec. 2	850							RHD
19	May 29	3,500	3.2	+	0.9	9.8	406	2.9:2.3	RHD
	June 21	1,400							
	June 30	1,500	2.8	+	1.2	11.4	219	3.5:3.0	
	July 15	920	3.0	—	1.4	8.3	172	3.8:3.0	
20	Aug. 25	700	1.5	—	0.8	6.9			CHD
	Sept. 14	570							
21	May 29	560	0.9	+	3.8	2.7	135	2.2:3.0	AHD
22	June 4	500							CHD
23	June 22	500	0.6	++	3.1	9.6	129	3.3:2.7	Constrictive pericarditis
24	Aug. 16	1,100						3.3:3.1	RHD
25	Oct. 15	680		—	3.1		197	4.2:3.6	RHD
26	Aug. 28	500		+	2.0		173	2.6:4.0	AHD
27	June 5	500	0.9	+	1.5	4.0		4.0:2.1	RHD
28	Nov. 15	960	1.0	+	2.5	2.9	155	3.0:3.0	AHD

* CHD indicates congenital heart disease; RHD, rheumatic heart disease, and AHD, arteriosclerotic heart disease.

Similar observations were made on a woman, aged 26, with congestive heart failure due to rheumatic valvular disease. Throughout the whole period of observation she was in severe heart failure with generalized anasarca and marked hepatomegaly. On July 3, 1957, when the first serum cyanocobalamin examination was performed, there was marked hepatomegaly, the right lower edge reaching the right iliac crest. The serum cyanocobalamin was 2,700μμg. per milliliter, and it came down on July 14, 1957, to 1,800μμg. after treatment with digitalis and mercurials, coinciding with a moderate reduction in size of the liver. The patient was examined subsequently on several occasions, and the serum cyanocobalamin was found to be continuously high,

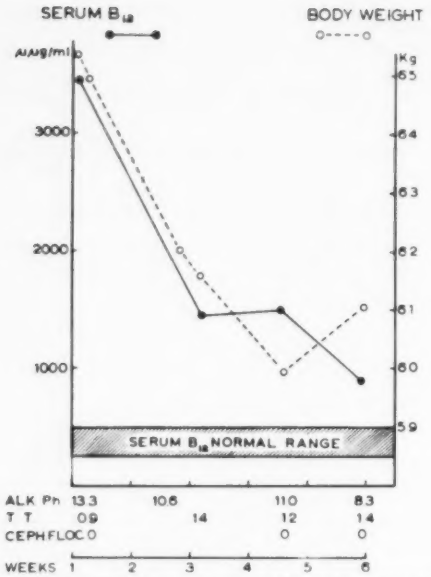

Fig. 1.—Serial serum cyanocobalamin (vitamin B_{12}) determinations in a patient with severe congestive heart failure. Note the parallel decrease of body weight and serum cyanocobalamin content.

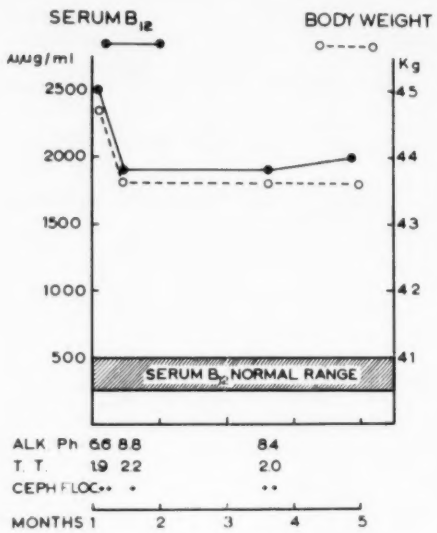

Fig. 2.—Serial serum cyanocobalamin (vitamin B_{12}) determination in a patient with severe congestive heart failure resistant to treatment.

the degree of cyanocobalamin elevation corresponding to the degree of heart failure and hepatic engorgement (Fig. 2).

On the other hand, a progressive gradual increase in the serum cyanocobalamin concentration was seen in a female patient, aged 42, who was suffering from mitral stenosis and insufficiency. When examined on July 10, 1957, in the outpatient department, she complained of increasing dyspnea and pressure in the epigastrium and loss of appetite during the last fortnight. The liver was found to be enlarged, the left liver border reaching 8 cm. below the left costal margin. The serum cyanocobalamin was within normal limits, 480 $\mu\mu$g. per milliliter. During the following three weeks the degree of hepatic congestion and size of the liver increased, with a concomitant rise in the serum cyanocobalamin concentration to 760 $\mu\mu$g. and then to 1,030 $\mu\mu$g. per milliliter.

As seen in the Table, the commonly used liver-function tests were only slightly altered. Moderate elevation of serum bilirubin, up to 4 mg., was encountered in some patients. In all these patients the serum cyanocobalamin concentrations were increased. The thymol turbidity and flocculation tests were negative, as a rule, in almost all patients, whereas the cephalin flocculation test was positive in some. Moderate to severe hypoalbuminemia was found in severe long-standing congestive heart failure. The most frequent biochemical alteration found was the increase of alkaline phosphatase. In all patients with increased alkaline phophatase values, except for a case with constrictive pericarditis, the cyanocobalamin was found to be elevated.

Postmortem examinations performed on Patients 6, 8, 10, and 23 disclosed severe chronic passive congestion of the liver.

Comment

The frequent association of congestive heart failure with increased serum cyanocobalamin levels may be explained by the development of anatomical changes in the liver architecture. These consist mainly of centrilobular necrosis, resulting from a com-

bination of hepatic anoxia and hemorrhages from the distended sinusoids due to the increase in the venous pressure. It is known that the longer the duration of heart failure the greater the underlying damage to the liver. It is not surprising, therefore, that the highest levels of serum cyanocobalamin were found in patients with long-standing heart failure. The absence of serum cyanocobalamin elevation in the patient with constrictive pericarditis could possibly be explained by the fact that in this case extreme systemic venous congestion was present during an unusually long period and treatment with mercurial diuretics began seven years prior to the present study. It might well be that the cirrhotic liver was losing large amounts of cyanocobalamin, which were excreted through the urine. Determination of the urinary excretion of cases with excessive diuresis showed actually increased amounts of the vitamin in the urine.

In acute liver damage, whether of viral [1-4] or chemical [3] origin, the rise of serum cyanocobalamin is temporary and returns either gradually or rapidly to normal levels. In prolonged heart failure persistent cyanocobalamin elevation may be found, as shown in Patients 2 and 4. Persistent high serum cyanocobalamin levels were also found in patients with malignant liver metastases,[6] since in this condition, as in heart failure, the underlying process causing dissolution of liver cells and responsible for the rise is continuously present.

Lieberman et al.[9] reported on serum transaminase levels in moderate to severe right heart failure. In only 3 out of 14 patients was the serum transaminase level found to be slightly elevated, and in these 3 patients a gradual drop to normal levels occurred as compensation was obtained. Chinsky and Sherry [10] found normal serum transaminase activity in 26 cases with chronic congestive failure.

In view of the fact that the commonly used liver-function tests, including serum transaminase, are negative in chronic passive congestion of liver, it seems that serum cyanocobalamin estimation is a more sensitive test of hepatocellular damage in heart failure. Fluctuations in the concentrations of serum cyanocobalamin found in prolonged heart failure may serve as an index of the degree of anoxia and hepatic necrosis.

Summary

Serum cyanocobalamin (vitamin B_{12}) activity was estimated in 28 patients suffering from severe chronic congestive heart failure. Elevated serum cyanocobalamin levels were found in 23 of them, while the commonly used hepatocellular function tests were usually normal. The serum cyanocobalamin levels decreased considerably in cases where compensation was attained.

The serum cyanocobalamin concentration in chronic congestive heart failure may serve as an index of the degree of hepatic damage.

Mrs. Mala Jablonska provided technical assistance.

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Failure of Oral Therapy in the Maintenance of Pernicious Anemia

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Introduction

Oral administration of cyanocobalamin (vitamin B_{12}) and intrinsic factor derived from hog stomach is known to be effective in producing remissions in patients with pernicious anemia in relapse. However, the efficacy of maintenance therapy with such preparations has been more difficult to evaluate. Short-term studies have indicated that satisfactory remission can be maintained on an oral preparation containing both cyanocobalamin and intrinsic factor.[1] Likewise, massive oral doses of cyanocobalamin without intrinsic factor may maintain patients with pernicious anemia in remission.[2-4] Since it has been observed that it may take several months to years for some patients with pernicious anemia to relapse, evaluation of a treatment program should be based upon a long-term study. The purpose of the present report is to compare the effectiveness of an oral preparation with that of parenteral cyanocobalamin in the management of pernicious anemia over a three-year period.

During the observation period it became apparent that, in the dosage schedule employed, hematologic relapses on oral therapy developed. It seemed desirable, therefore, to study the absorption of radioactive cyanocobalamin in the presence of intrinsic factor in order to elucidate the mechanism by which the oral preparation failed to maintain a satisfactory hematologic remission.

Materials and Methods

Included in the study were 39 patients with pernicious anemia. The diagnosis had been established previously by the presence of (1) macrocytic anemia, (2) histamine-fast achlorhydria, and (3) a megaloblastic bone marrow. The majority of these patients had been followed for several years in the outpatient department of University Hospitals of Cleveland and had responded to some form of anti-pernicious-anemia therapy. They were in complete hematologic remission at the beginning of the study.

The preparation tested was an oral tablet containing 7.5μg. of cyanocobalamin and 18 mg. of an intrinsic factor concentrate derived from hog stomach.* The patients were instructed to take 2 tablets each morning before breakfast, for a daily dose of 15μg. of cyanocobalamin and 36 mg. of intrinsic factor concentrate. This amount constituted 1 U. S. P. unit, as determined by a previous assay. Selection of patients to receive this preparation was made on the basis of ability to cooperate and the absence of severe neurological manifestations. A total of 16 patients were selected for treatment with the oral preparation. A group of 23 patients continued to receive parenteral cyanocobalamin, 30μg. every four weeks, and served as controls. Patients were followed in the hematology clinic of the outpatient department of University Hospitals of Cleveland. They were observed at two- to four-week intervals, and complete blood cell counts and hematocrits were obtained at each visit.

The urinary excretion test was essentially that described by Schilling.[5] Co^{60}-labeled cyanocobalamin, in amounts of 0.5μg., with a specific activity of 1.05μc. per microgram, was diluted with water and was given orally to patients who were in a fasting state. This was followed in one hour by a "flushing dose" of 1 mg. of nonradioactive cyanocobalamin given intramuscularly, and all urine was collected for 24 hours. The radioactivity in an aliquot of urine was determined in a well type scintillation counter with a thallium-activated sodium iodide crystal. The results were expressed in per cent of administered dose excreted in a 24-hour period.†

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* Intrinase, supplied by The Upjohn Company.

† Calculation:

$$\% \text{ excreted} = \frac{\text{counts/min. in 24-hr. urine}}{\text{total counts/min. administered}} \times 100$$

TABLE 1.—*Results of Oral and Parenteral Therapy*

Cyanocobalamin	Cases, No.	Relapses, No.
Parenteral	23	0
Oral	16	5

Results

The results of a three-year observation period are summarized in Table 1. In the control group of 23 patients who continued to receive parenteral cyanocobalamin, there were no relapses. During the same three-year period, 5 of the 16 patients treated with an oral preparation developed an unequivocal hematologic relapse. There were no lingual or neurological relapses.

The duration of oral therapy prior to relapse in these five patients is shown in Table 2. Patient 1 developed a relapse after only 6 months of therapy, while in the remaining four patients, relapse occurred after 18 to 33 months of oral therapy. The fall in hematocrit values during this time ranged from 4% to 13%, with a mean fall of 9.5%. The hematocrit value prior to oral therapy represents an average of three consecutive determinations, and the hematocrit value at the end of oral therapy was the average of at least two determinations, one week apart.

In two patients who had relapsed (Patients 3 and 4), the daily oral dose was increased twofold without any rise in hematocrit. After the intramuscular administration of cyanocobalamin the hematocrit values returned to normal levels in all five patients and was preceded by a reticulocyte response commensurate with the degree of anemia.

TABLE 2.—*Failures with Oral Therapy*

Patient No.	Duration of Oral Therapy, Mo.	Hematocrit Value: Prior to Oral Therapy	Hematocrit Value: End of Oral Therapy	Hematocrit Value: After Parenteral Cyanocobalamin
1	6	41.5	28.5	42
2	18	42	38	44
3	18	45	35	44
4	26	38.5	31.5	40
5	33	44.5	33	45

The urinary excretion of orally administered radioactive cyanocobalamin in the patients who relapsed on oral therapy is shown in Table 3. The 24-hour excretion of Co^{60}-cyanocobalamin in these five patients was 1.0% or less without intrinsic factor. In the presence of 18μg. of intrinsic factor concentrate ‡ no enhanced excretion occurred. Even when four times the amount of intrinsic factor concentrate (72 mg.) was administered, there was no increased excretion in three of the five patients. Two of the patients (Patients 3 and 5) excreted 9.6% and 6.9%, respectively, with this dose. The three patients who failed to respond to 72 mg. of intrinsic factor were tested with another more purified preparation of a highly active fraction derived from hog stomach. The urinary excretion test still showed no significant change with this preparation. In these same three patients, the administration of 100 ml. of normal human gastric juice was accompanied by a marked increase in the urinary excretion of radioactive cyanocobalamin (Table 3). Of the 11 patients on oral therapy who did not relapse, 10 were tested with use of the same amount of intrinsic factor as was used in the oral preparation. When 18 mg. of intrinsic factor was administered with the radioactive cyanocobalamin, three additional patients showed no increased excre-

TABLE 3.—*Urinary Excretion Tests in Five Failures on Oral Therapy*

Patient No.	Administered Radioactivity in Urine, % *: Without I. F.	18 Mg. I. F.	72 Mg. I. F.	NHGJ †
1	0.0	0.4	1.3	24.0
2	0.6	0.5	0.6	9.0
3	1.0	1.6	9.6	--
4	1.0	1.4	1.7	7.8
5	0.8	0.5	6.9	--

* I. F. indicates intrinsic factor concentrate; NHGJ, normal human gastric juice.

‡ Supplied from same source as in the commercial preparation.

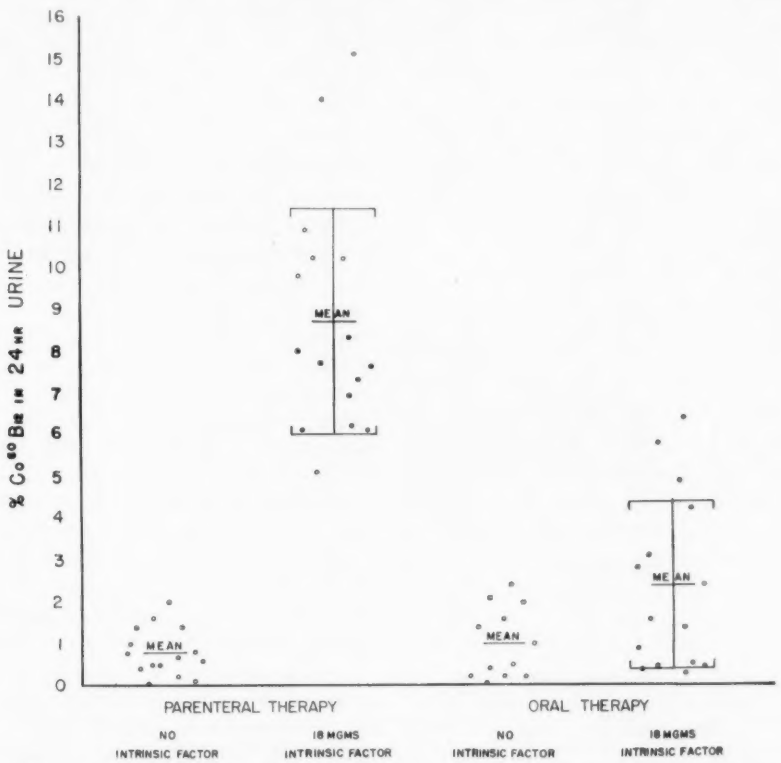
TABLE 4.—*Comparative Effect of Prolonged Oral Therapy on Urinary Excretion Test Co^{60}-Cyanocobalamin*

Treatment	No. Tested	Amount I. F.,* Mg.	Urine Radioactivity, % Range	Mean
Oral	15	18	0.3-6.4	2.4
Parenteral	16	18	5.3-15.1	8.7

P is less than 0.001.

* I. F. indicates intrinsic factor concentrate.

tion of radioactivity. The remaining seven patients exhibited a significant rise in the urinary excretion of cyanocobalamin with this amount of intrinsic factor. However, when the groups as a whole are compared, the oral treatment group excreted less Co^{60}-cyanocobalamin in the urine than the parenterally treated group with the same amount of intrinsic factor (Table 4 and Figure). In the patients who were maintained on oral cyanocobalamin and intrinsic factor, the average of the urinary excretion test was 2.4%, with a standard deviation of ±2.0%. In comparison, patients who had received only parenteral cyanocobalamin had an average urinary excretion test value of 8.7% of the administered dose, with a standard deviation of ±2.7%. This difference is illustrated in the Figure, which compares the CO^{60} excretion in orally treated and parenterally treated patients with and without intrinsic factor. The probability that the difference in excretion of radioactive cyanocobalamin in the presence of



Effect of prolonged oral therapy of pernicious anemia on urinary excretion of Co^{60}-cyanocobalamin. Each circle represents the 24-hour urinary excretion test of Co^{60}-cyanocobalamin in a single patient with and without the oral administration of intrinsic factor concentrate. The mean value and one standard deviation are shown.

18 mg. of intrinsic factor could occur by chance is $P=0.001$.§

Comment

It is apparent that cyanocobalamin, when administered orally in the presence of a commercial source of intrinsic factor, is not satisfactory in the dose employed for maintenance therapy of pernicious anemia. The duration of oral therapy prior to relapse varied from as short as 6 months to as long as 33 months. It is possible that more patients would have relapsed if the treatment period had been extended beyond three years, especially in view of the fact that three additional patients appeared to be refractory to intrinsic factor concentrate. In two of the five patients who relapsed, increasing the daily dose twofold failed to produce a rise in hemoglobin and hematocrit values. Furthermore, in one of these two patients, even quadrupling the daily dose did not induce a remission.

It is of interest that, although hematologic relapse occurred in these patients, there were no lingual or neurological relapses. In a group of patients on oral therapy, reported by Blackburn et al.,[6] hematologic failures were common after one year and one patient developed a neurological and lingual relapse after only nine months of therapy. However, the daily dose of cyanocobalamin in that series was less than one-half the amount of vitamin employed in the present study. Thus, the amount of cyanocobalamin administered daily, as well as body stores of cyanocobalamin may be important determinants in the type and rapidity of relapse.

The mechanism by which these failures develop is not known. The results of the urinary excretion tests indicate that prolonged administration of heterologous intrinsic factor may result in the development of a refractory state to intrinsic factor concentrate. Unfortunately, urinary excretion tests with the same intrinsic factor as incorporated into the oral tablets were not performed at the beginning of the study. However, when the urinary excretion tests of the orally treated group are compared with those of the parenterally treated groups, as shown in the Figure, the differences appear statistically significant. Thus, in the presence of the same amount of intrinsic factor, less cyanocobalamin was absorbed in patients maintained on oral therapy than in patients who had received only parenteral cyanocobalamin. This suggests that the former group had acquired a resistance to the normal physiologic action of intrinsic factor.

The urinary excretion data in this report represent only that amount contained in the first 24-hour urine collection. Ellenbogen et al.[7] have shown that significant amounts of radioactivity may be excreted in the second 24-hour period if another "flushing dose" of nonradioactive cyanocobalamin is given. Therefore, one must consider the possibility that the decreased excretion values found in the orally treated group were due to delayed excretion. However, in three of the five patients who relapsed on oral therapy, no additional radioactivity was excreted in the second 24-hour period. The other two patients were not tested after 24 hours. Furthermore, two patients who did not relapse on oral therapy but who excreted less than 1.0% of the cyanocobalamin with 18 mg. of intrinsic factor showed no further radioactivity in the urine after a second "flushing dose." Therefore, in all probability the reduced effect of intrinsic factor found in the orally treated group was not due to slow absorption or delayed excretion.

In the group in whom commercial intrinsic factor failed to enhance absorption of cyanocobalamin, restudy up to three years after discontinuation of oral therapy still demonstrated no change from the original observation on the urinary excretion tests. It is possible, then, that the acquired

§ Statistical analysis of the data was made by Dr. Arthur Littell, of the Department of Preventive Medicine, at Western Reserve University School of Medicine, Cleveland.

refractory state to heterologous intrinsic factor represents a permanent alteration. The development of this refractory state may be the result of repeated exposure of the gastrointestinal mucosa to heterologous intrinsic factor. The duration of exposure necessary for developing the refractory state is not known, but, in view of the variable time of relapse, it may range from a few weeks to several months.

Schwartz and his colleagues [8] first noted the reduced effect of hog intrinsic factor following oral treatment after six months to four years. The oral capsule used in their studies appeared to contain a crude intrinsic factor preparation. They compared the urinary excretion values of these patients to untreated pernicious anemia and found results comparable to our observations. They postulated a "mucosal block." Lowenstein et al.[9] have reported similar observations and noted an even higher percentage of relapse on oral therapy. In their group, 19 of 36 patients reverted to a megaloblastic marrow on oral therapy and four patients developed a definite fall in peripheral blood values. The majority of these patients received less than 10μg. of cyanocobalamin daily. It is possible that some of these relapses were related to low doses of oral cyanocobalamin rather than failure of the intrinsic-factor preparation. The time required for development of the refractory state was not determined in their studies. However, Stokes and Pitney [10] have reported a case in whom refractoriness to heterologous intrinsic factor appeared after only eight weeks of oral therapy. It is not possible to determine from our data whether a reduction of the absorption of cyanocobalamin with intrinsic factor concentrate persists or is merely a stage in the development of a complete block to heterologous intrinsic factor.

The preparation of intrinsic-factor concentrate used in these studies contained a considerable amount of blood-group substance A. This is not surprising, since porcine gastric mucosa is a commercial source of A-substance. This suggests the possibility of blood-group substances being involved in the development of the refractory state. However, precipitin reactions, utilizing the intrinsic factor concentrate of the antigen and the sera of the patients who relapsed as the source of antibody, were negative. In addition, the blood types of the five patients who relapsed on oral therapy were as follows: two were A; two were O, and one was AB. This occurrence of different blood groups would make the role of A-substance in the development of the refractory state unlikely. The failure to demonstrate precipitating antibodies in the patients sera and to implicate A-substance by no means excludes the possibility of some antigen-antibody type of reaction as the basis for the refractoriness to heterologous intrinsic factor.

It has recently been shown by Schwartz [11] that the serum of patients with pernicious anemia who have been treated with an oral preparation contains an intrinsic-factor-inhibiting substance. This was not, however, an invariable effect, and this inhibition occurred in the sera of patients in whom no mucosal block to heterologous intrinsic factor could be demonstrated. On the other hand, these observations, if confirmed, may strengthen the concept of an antigen-antibody reaction as the basis for the development of the refractory state to intrinsic factor.

Further studies are now in progress to elucidate the mechanism by which this refractory state occurs, and it is hoped that they will shed some light on the mode of action of intrinsic factor.

Summary

During a three-year observation period, 5 of 16 patients with pernicious anemia relapsed on an oral preparation containing both cyanocobalamin (vitamin B_{12}) and intrinsic factor. There were no neurologic or lingual relapses.

The patients who relapsed showed a marked reduction to the effect of commercial intrinsic factor enhancing intestinal ab-

sorption of cyanocobalamin. Even the patients on oral therapy who did not relapse showed a diminution in response to intrinsic factor. It is probable that this represents an acquired refractory state to heterologous intrinsic factor, thereby reducing the effectiveness of the oral preparation. Parenteral therapy of pernicious anemia with cyanocobalamin is still the treatment of choice.

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Case Reports

Hypnosis in the Termination of Hiccups Unresponsive to Conventional Treatment

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Although it is agreed that there is no satisfactory working hypothesis as to the underlying nature of hypnosis,[1-3] many observations supporting the influence of hypnosis on physiological processes have been documented. These observations include the effect of hypnosis on cough,[4] on electrocardiogaraphic changes,[5] and on the extent of allergic cutaneous responses.[6,7] The normal plantar flexion response to stimulation of the sole of the foot can be changed to a pathologic response (Babinski's sign) through hypnotic age regression.[8] The effect of hypnotic suggestion in modifying gastrointestinal disturbances has been noted repeatedly.[9]

Previous case reports[10,11] support the contention that hiccups occurring during the course of myocardial infarction is a poorly tolerated complication. In view of the serious import of this complication, the apparent success of a new therapeutic adjunct, following the failure of conventional therapy, would appear to justify the reporting of this case. Additional speculation as to the possible influence of hypnosis on the process of hiccups is provoked.

An exhaustive review of the literature fails to reveal any previous record of successful termination of hiccups following a single application of hypnotic suggestion.

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Chief Medical Resident (Dr. Bendersky) and Intern (Dr. Baren), from the Department of Medicine, The Hahnemann Medical College and Hospital of Philadelphia. Present address: Children's Hospital of Philadelphia (Dr. Baren).

Report of Case

A 50-year-old man was admitted on Nov. 30, 1957, to the medical ward of Hahnemann Medical College Hospital, with a history of severe chest pain of 12 hours' duration. The patient had been in his usual state of health until two weeks prior to admission, when he started to experience precordial, nonradiating chest pain, lasting 5 to 10 minutes and most evident after meals or when walking any distance. The patient had had the same symptom complex five years previously, and an electrocardiogram done then showed no abnormalities. The night prior to this admission, the patient experienced a severe, prolonged, pressing, constant, retrosternal chest pain which radiated down both arms. His family physician administered meperidine (Demerol), which ameliorated the pain to some degree.

Physical examination showed the patient to be a well-developed, well-nourished man in obvious mild distress; temperature 99 F, pulse 100, respirations 20, and blood pressure 100/72. The head and neck were normal. The lungs were clear to percussion and auscultation. A tachycardia of 100 was evident. There were no murmurs; the heart sounds were normal; there was no gallop rhythm. The remainder of the physical examination was essentially within normal limits.

The electrocardiogram revealed typical changes of an acute coronary occlusion with infarction of the diaphragmatic portion of the left ventricle and evidence of an old infarct involving the midanterior portion of the left ventricle. Routine laboratory work was unremarkable.

The patient was placed on bed rest, a 0.5 gm. salt diet, morphine sulfate for pain, heparin and bishydroxycoumarin (Dicumarol), oxygen via nasal catheter, and long-acting barbiturates during the day and secobarbital (Seconal) at bed time. On his second hospital day, the patient's blood pressure dropped slowly to 80-84 systolic and signs of cardiac decompensation developed in association with clinical signs and symptoms of shock. He was digitalized with digoxin orally in 12 hours, and methoxamine (Vasoxyl) and levarterenol (*l*-norepinephrine [Levophed]) were administered in-

travenously, the latter being required for the subsequent 16 days. His pain subsided, his mental outlook became brighter, and the urinary output remained normal.

On Dec. 19, 1957, 20 days after admission, he started to hiccup. This was infrequent and transient at first, but within 24 hours had become fairly severe, recurring at intervals of one to five minutes and resulting in extreme exhaustion of the patient. The usual routines of tongue traction, breathing in a paper bag, supraorbital pressure, inhalation of 5% carbon dioxide and 95% oxygen, and sedation were tried. These procedures were attempted singly and in various combinations for 24-48 hours but gave very little relief at first (intervals between episodes became slightly more prolonged) and finally no relief at all. At the same time, the patient became extremely apprehensive and the retrosternal pain returned. The longer the hiccups continued, the more fatigued the patient became, and it became evident that his condition was deteriorating rapidly.

Chlorpromazine (Thorazine), in 25-50 mg. doses intramuscularly, was given periodically as required. At first this helped somewhat, stopping the hiccups for periods of 2 to 4 hours, but after 24-36 hours this was no longer effective. Thereupon all previous therapy directed at the hiccups was discontinued. He was placed on a regimen of chlorpromazine, 50 mg. every four hours around the clock. This was given alone and then in combination serially with atropine subcutaneously, other antispasmodics, diphenhydramine (Benadryl), chloral hydrate, papaverine, dimenhydrinate (Dramamine), and meperidine. In association with these medications, traction on the tongue and other vagal stimuli were again tried. Other methods, such as adequate trials of intermittent 95% oxygen and 5% carbon dioxide again, fruit juice containing procaine, and barbiturates, were interspersed with the chlorpromazine, but the hiccups continued. During this time the patient became lethargic and confused; there was an exacerbation of chest pain not responding to pentaerythritol (Peritrate) tetranitrate. The probable cause of the hiccups was considered to be diaphragmatic irritation secondary to the infarct, but other possibilities, such as pulmonary infarct, renal disease, and pneumonitis, were likewise considered. On Dec. 23, 1957, after four days of almost constant hiccuping, the patient was given a trial of deep sedation. Amobarbital sodium in doses of 250 mg. was given as frequently as hourly intervals along with the chlorpromazine. This only served to make the patient extremely confused, and he developed hallucinations and delusions; so the amobarbital was stopped within several hours. Phrenic nerve block, gastric lavage, and quinidine were considered but not used.

On Dec. 28, 1957, after eight days of hiccuping with progressive exhaustion, it was decided to try hypnotic suggestion. The previous therapy was discontinued for 12 hours, during which time the patient was observed to be reasonably alert and cooperative despite the continued hiccups (at a frequency of 1 to 20 minutes). A hypnotic trance was induced by one of us (G. B.) over a period of forty-five minutes at a time when the patient was oriented as to the purpose of the procedure. The hand-levitation and hand-clasp techniques were used to the depth of successful glove-hand anesthesia. Thereupon the patient was advised to "breathe naturally in a relaxed way," and that "with each breath the breathing trouble would become less difficult until the hiccups would disappear completely, leaving a comfortable, easy breathing cycle." Then a posthypnotic suggestion was introduced that the hiccups would cease completely upon closing the door by the physician. This proved to be successful. Except for two hiccups which occurred several hours later, the hiccups failed to return. The remainder of his convalescence was uneventful. On Jan. 24, 1958, he was discharged to the care of his family physician.

Comment

Although the mechanism for the production of hiccups in diaphragmatic or posterior-inferior myocardial infarction has not been definitely established, an appreciation of the local anatomy allows the possibility of pleural irritation as the underlying stimulus. However, that direct irritation may not be the only factor is suggested [11] by the finding of hiccups in anterior myocardial infarctions in the absence of posterior-inferior involvement. In considering the innervation of the heart and the many ramifications of the cardiac plexuses, previous authorities [11] have felt that whatever the initial stimulus is, the basic process may be reflex in origin. The heart apparently receives its innervation from the superficial and deep cardiac plexuses which connect with the vagus, spinal accessory, crucial sympathetic trunks, and cervical segments of the spinal cord. Samuels [12] has thoroughly reviewed this pertinent anatomy.

The stimuli to the "respiratory reflex" of hiccup may arise from the distribution of the phrenic nerve afferents, from electro-

lyte disturbances, from pathological processes involving the respiratory center, and, admittedly, from obscure or undemonstrable sources.[13]

Among the many factors known to influence the induction of hiccups, psychogenic factors may play an important role. That the mechanism in our case may have been largely psychogenic is supported by previous studies which have elicited such underlying psychodynamic factors as fear of heart defect[14] and sudden reception of psychotraumatic information.[12] It has been stated: "Psychogenic influence plays a great part in all but a very few cases. . . . Even in the presence of definite causative disease, the psychogenic status of the patient must be thoroughly investigated."[12] However, in our case, no attempt was made hypnoanalytically to reveal information which would suggest this nonorganic etiology.

In turn, one questions the mechanism by which hypnosis might have been effective in the resolution of hiccups. First, indirect evidence may be invoked to support the theory of cortical-hypothalmic control. The work of Doupe[15] and his associates has demonstrated that hypnotically induced anesthesia is capable of inhibiting the vasoconstrictor response to painful stimuli. It would be pure conjecture, though, to apply this by analogy to the hypnotic anesthetization of the phrenic afferents. In discussing their case of long-term (10 treatments in five months) use of hypnosis in a patient whose hiccups were associated with metastatic carcinoma, Kirkner and West[16] felt that hypnosis may inhibit the cerebral cortex, as seen by the influence of voluntary action, relaxation, and sleep on the magnitude of reflexes. Kuntz[13] and Gillilan[17] have reviewed the present status of the corticohypothalamic connections and leave the impression that, as it relates to the influence of hypnosis on the diaphragm, very little, if anything, is known. Second, a likely explanation lies in the well-known success of hypnotic suggestion to suppress psychogenically induced symptom formation.[2] The empirical fact that symptom suppression can be secured in this manner, in turn, deserves much comment which is not in the realm of this discussion. Third, it must be admitted that the hiccups in our case may have resolved spontaneously as a coincidence with the hypnotic trance.

The general use of hypnosis for merely eliminating psychosomatic manifestations cannot be endorsed and may in fact be highly dangerous. With the recognition of the gravely prognostic sign of hiccups associated with myocardial infarction, this case warranted the thorough trial of the multiple therapeutic measures (repeatedly given before discarding them), including the use of hypnosis.

Despite previous enthusiastic reports in the successful use of chlorpromazine in hiccups, it is noteworthy that in our case, as in a few recently reported,[18] in the doses given, this particular drug failed even after prolonged use and in association with barbiturates and narcotics.

Summary

A case is presented of a patient with prolonged hiccups seriously complicating a myocardial infarction, with the subsequent termination of hiccups under hypnosis after failure with conventional therapy (vagal stimuli, antispasmodics, chlorpromazine, antihistamines, intermittent carbon dioxide inhalation, narcotics, local anesthetics, and barbiturates).

Since one of the explanations for the effectiveness of hypnosis in this case is by virtue of the psychogenic etiology in hiccups, it is suggested that in cases of "intractable hiccups," despite the elicitation of specific organic causes, the psychogenic factor may predominate and allow hypnotic resolution.

Brief discussion is presented of proposed mechanisms of hiccups production with relation to hypnosis for the purpose of revealing inadequacy of our present knowledge in this field.

Dr. James B. Donaldson, Chief of Medical Service C, gave advice in the management of this patient, and Dr. C. Arvanitis, Chief Surgical Resident, suggested the use of hypnosis.

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Perirenal Hematoma Secondary to Polyarteritis Nodosa

Report of a Case and Review of the Literature

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Since the time Rokitansky first reported, in 1852, his new disease of blood vessels with a clinical and pathological study of three cases and Kussmaul and Maier, in 1866, provided a complete description, including histological features, of the disease which they termed periarteritis (polyarteritis) nodosa, several hundred cases have subsequently been described in the English literature and, including foreign sources, perhaps well over a thousand. Despite this ever-growing accumulation of case material, the etiology, pathogenesis, and treatment of this disease remain to be elucidated. Excellent reviews of current viewpoints regarding the nature of polyarteritis and characterization of clinical features, as gleaned from large series of cases, have been presented by Nuzum and Nuzum,[1] Mowrey and Lundberg,[2] and Rose and Spencer.[3]

Perirenal hematoma as a complication of polyarteritis nodosa was first reported by Schmidt,[4] in 1908. Since that time, 24 other cases [5-28] have appeared in the English and foreign literature. Two of these cases [27,28] described only pathologic findings and are not considered with the others in the discussion below. An additional case report follows.

Report of Case

A 39-year-old white male janitor of Italian birth was admitted to the medical ward of the Philadelpia General Hospital on April 25, 1957, with a chief complaint of muscle and joint pains.

He gave a history of being in his usual state of good health until 10 days prior to admission, at which time he noticed a severe frontal headache accompanying the onset of persistent malaise. The headache remitted within a few hours, but thereafter the patient developed muscle pains in the posterior cervical area, which, in the course of the next few days, gradually involved the muscles of the shoulder girdles, forearms, thighs, and legs and the joints of the shoulders, wrists, and knees. These pains were of a sharp nature, at times asymmetrical and at other times symmetrical, and were aggravated principally by pressure and motion. The patient also complained of fever with occasional chills and noticed slight anorexia. There were no other symptoms related to the gastrointestinal tract. A recent onset of occasional nose bleeds was noted. There was no history of malaria, rheumatic fever, ingestion of raw pork, or contact with rats. An injection of penicillin was purported to have been given two weeks earlier. The patient denied excessive alcohol consumption and indicated that his dietary intake was very adequate. No other history of drug or serum administration was elicited.

Physical examination at the time of admission revealed a normally developed, well-nourished Caucasian man with a blood pressure of 150/100, pulse 99, respirations 18, temperature 100 F. There was a slight vesicular eruption about the lips. Heart and lungs were normal on clinical examination. The liver was enlarged, with the upper border percussed at the right fourth anterior interspace and the lower edge palpated 4 cm. below the right costal margin. There were numerous petechiae over both anticubital fossae and the circumferential area of both ankles. There were several spider angiomata over the upper chest and neck. Marked muscle tenderness of the neck, forearms, thighs, and legs was elicited on pressure, without evidence of swelling or erythema. Complete neurological examination revealed only bilateral Hoffmann's sign and hyperesthesia of the plantar surface of both feet on tactile stimulation.

Initial laboratory studies revealed a hemoglobin of 14.1 gm. % and a white blood cell count of 7,350, with 79% neutrophils, 15% lymphocytes, 4% monocytes, 1% eosinophils. Total eosinophil count was 210 per milliliter. Platelet count was 320,000, with a bleeding time of 2 minutes 6 seconds and a clotting time of 3 minutes 53 seconds. The urine on admission had a specific gravity of 1.023, acid reaction, no protein or sugar, 0-2 WBC and 4-6

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RBC per high-power field. There were no casts. Sulfobromophthalein (Bromsulphalein) retention at the end of 30 minutes was less than 5%. Total serum bilirubin was 0.7 mg. %. Alkaline phosphatase was 5.3 Bodansky units. There was a total serum protein of 7.8 gm., with 4.5 gm. of albumin and 3.3 gm. of globulin per 100 ml. Serum cholesterol measured 160 mg. %, with 49% esters. The prothrombin time was 36%. There was a 4+ cephalin flocculation, with a thymol flocculation and thymol turbidity of 0. The blood urea nitrogen was 14 mg. %, and the fasting blood sugar 87 mg. %. The blood VDRL and Kolmer tests were negative. Examination of the spinal fluid revealed normal cells, protein 44 mg. %, sugar 18 mg. %, and chloride 68.5 mg. %. It was negative for culture of pyogenic organisms or acid-fast bacillus. The colloidal gold curve was 1233210000. Throat culture revealed Diplococcus pneumoniae. Five blood cultures and one urine culture resulted in no growth. Stool culture was negative for Salmonella or Shigella. Cysts of Giardia lamblia were found in the stool, which was negative for occult blood. Heterophil and febrile agglutinins were negative, as were two L. E.-cell preparations. Antistreptolysin O titer was within normal range. P. P. D. No. 1 was positive after 48 hours. Skin test for Trichinella sensitivity was negative. Serum studies for lymphocytic choriomeningitis and poliomyelitis were negative.

An electrocardiogram was normal. Marrow examination revealed granulocytic hyperplasia and minimal hemosiderosis, which were thought to represent a response to a toxic inflammatory process.

A chest film on admission revealed no abnormalities. An upper gastrointestinal series and scout film of the abdomen, in an attempt to demonstrate possible abdominal masses, only substantiated the hepatomegaly noted on physical examination. The spleen was not discerned.

Biopsies of the scalene and axillary nodes, deltoid and gastrocnemius muscles and an open biopsy of the liver revealed only nonspecific lymphoid hyperplasia of the nodes.

After a week of hospitalization bilateral ankle clonus was noted, which was sustained in character on the left and unsustained on the right. No other neurological accompaniments developed with this finding. The calf muscles became noticeably atrophic and atonic shortly after admission, although the patient declined to ambulate owing to marked weakness. A slowly developing anemia was in evidence throughout the patient's hospitalization, from a level of 14 gm. % to 10 gm. %.

After the bacterial studies and biopsies had been performed, an empirical trial of sulfadiazine and later penicillin and streptomycin was instituted without effect on the patient's febrile course. On

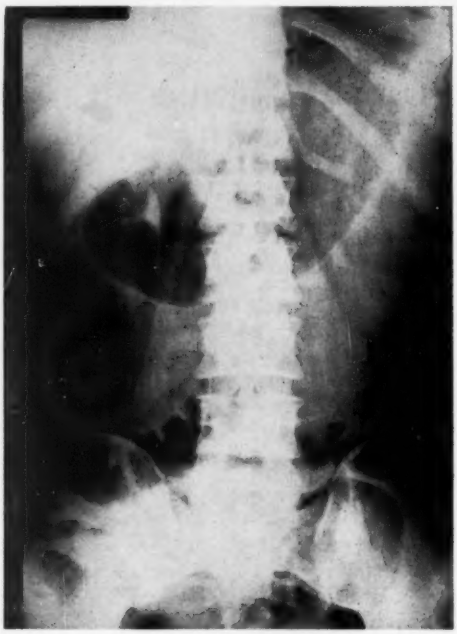

Fig. 1.—Left kidney does not visualize on intravenous pyelogram. Instead, a large mass is seen in the left flank, with its inner margin well delineated just lateral to the psoas shadow.

the 48th hospital day, the patient developed a severe pain in the left upper quadrant, which radiated around to the left costovertebral angle. There was marked muscle guarding in the left upper quadrant and absent bowel sounds. A mass was noted to be developing in size in the left upper quadrant with an overlying area of bluish discoloration of the skin. The patient gradually became hypotensive, with a drop in hemoglobin from 10 gm. % to 8 gm. %. A Stat. intravenous pyelogram (Fig. 1) revealed absent excretory function of the left kidney, which was thought to be greatly enlarged without obscuring the clearly defined psoas shadow. Urinalysis revealed innumerable red blood cells in the sediment.

During an induction of general anesthesia preparatory to an exploration of the left retroperitoneal area, the patient developed cardiac ventricular fibrillation. Immediate thoracotomy was performed, and resuscitative attempts were successful. The patient relapsed into a shock condition which did not respond to blood transfusions, vasopressors, or adrenal corticosteroids. He became anuric and died on the second postoperative day, June 14, 1957.

Necropsy was performed on June 15, 1957, by Dr. William Beckfield. Gross examination revealed

Fig. 2.—Frontal section through the midportion of the left kidney, revealing thrombus-containing aneurysms in the cortex, which also contains areas of infarction. A remnant of the perirenal hematoma extends around the superior pole.

bilateral multiple intrarenal aneurysms, measuring from 0.5 to 3.5 cm. in diameter, with intraaneurysmal thromboses, more numerous in the left kidney (Fig. 2). There was noted rupture of a left intrarenal aneurysm of the superior pole, with concomitant perinephric and retroperitoneal hematoma, estimated to be more than 1,000 cc. in amount, enveloping the left psoas muscle from its origin to its insertion and the left suprarenal gland. The cortex of the left kidney appeared almost entirely necrotic. The spleen was enlarged, weighing 420 gm. There was a small thrombus-filled saccular aneurysm of a branch of the splenic artery.

Other findings during gross examination included intrathoracic hemorrhage, pulmonary atelectasis of the left lung, and hemopericardium, which were complications of the thoracotomy wound and open cardiac resuscitive procedure.

Microscopic examination revealed lesions typical of polyarteritis nodosa involving the kidneys, adrenals, and spleen.

Comment

Although almost every organ has been found to be susceptible to the disease, it has been established by several investigators,[2,29-32] that the vascular lesions of polyarteritis are most frequently found in the kidneys, with 80% being the average tabulated occurrence. That the renal involvement results in clinical expression is suggested by the frequent incidence of abnormal urinary findings, the most predominant of which is albuminuria amounting to approximately 70% of case series.[1,2,30] These urinary abnormalities are most certainly reflections of direct renal involvement in the disease process rather than being incidental to a systemic wasting febrile disease. The former relationship is substantiated by Ralston and Kvale's observation that in 23 of 24 cases in which lesions of polyarteritis involving renal vasculature were noted at necropsy there had been abnormal urinary findings. In this case, however, it is interesting to note that four urinalyses performed at least several days apart during the patient's illness were entirely normal. The last normal urinalysis was performed eight days before the onset of the hemorrhage from the intrarenal aneurysm, which was then accompanied by gross hematuria. Of the twenty-one cases for which urinalyses are recorded in this series gathered from the literature, there are four [5,6,16,17] without urinary abnormalities. One urinalysis was recorded for three of these cases and two for the fifth during the course of illness. In those cases with more than one urinalysis recorded, varying degrees of abnormalities are noted and some with occasional normal findings, which leads one to surmise that if a diligent and persistent search is made for urinary pathology, such would be found when kidney involvement is present.

Owing to increasing awareness of this disease, the diagnosis is being inferred by clinical acumen more frequently, with definite confirmation dependent on concordant histopathological examination of biopsy tissue. Muscle biopsy, however, has been a somewhat disappointing means of establishing a positive diagnosis. The ex-

tent to which reliance on this procedure is unrewarding and often misleading is definitely assessed by Maxeiner et al.,[33] who found only 35% of the muscle biopsies to be positive in 26 subsequently proven cases of polyarteritis nodosa. Specimens were taken from symptomatic muscle groups when present. There were 65% false-negative biopsies. Millikan[34] estimates that only 20% to 25% of the biopsy results are positive in cases that later prove to be polyarteritis nodosa. In this case, biopsies of two different muscle groups were negative for evidence of the disease. Needle biopsy of the kidney, while potentially more hazardous in this disease owing to interruption of possibly existing aneurysms, might merit investigation by cognizance of the greater frequency of renal involvement.

The etiology of polyarteritis remains obscure, although the most widely accepted concept is that of a sensitivity reaction to certain bacteria, serums, vaccines, or drugs, with the sulfonamides, iodine, diphenylhydantoin (Dilantin), thiouracil, and penicillin being incriminated.[1] It has been generally accepted that the incidence of the disease has increased since the introduction of sulfonamides. Some authors, however, contend that the incidence is not increasing to an extent that might be expected if sensitivity to drugs is the predominant etiologic factor. Thirteen of the cases in this series have appeared since the introduction of sulfonamides for general clinical use, after 1939. No mention is made of their use in any of these cases except the one presently reported. Twelve cases occurred in a comparable 18-year period before the introduction of sulfonamides. Although such a comparison is interesting to note, the variables of case reporting and selection, among others, render these observations inconclusive. There are not as yet available data indicating case-incidence trends for this disease such as have been recently reported for lupus erythematosus, which is said to be ever more prevalent.[35] There is in this case a history of a penicillin injection given to the patient two weeks prior to the onset of symptoms. This is noteworthy owing to the purported relationship between penicillin sensitivity and polyarteritis nodosa. In the light of the foregoing, however, the exact significance is open to conjecture and awaits further clarification.

In the case reported by Canny,[15] the question was raised whether the hypertension occurring in the course of polyarteritis nodosa might be attributed to renal ischemia resulting from lesions in the arterial and arteriolar walls. Ralston[28] reports that in 17 of 20 cases of polyarteritis nodosa in which hypertension was present there were vascular changes of polyarteritis in the kidneys and that, conversely, hypertension developed in 17 of the 24 cases showing vascular lesions of polyarteritis in the kidneys. Rose and Spencer[3] concluded in their study that the development of hypertension in polyarteritis is associated with the healing stages of renal polyarteritis, that is, with fibrosis or ischemic infarcts. Among the 48 patients whose blood pressure remained normal in their study, recent renal polyarteritis and glomerulitis were common but healed lesions were rare. Of the 17 patients who were observed to develop hypertension during the course of the disease, all but 3 showed healed renal polyarteritis or glomerulitis at necropsy. In this series of polyarteritis leading to perirenal hematoma, 16 of the 21 cases with recorded blood pressure readings were elevated at least above 140/90. No mention of infarction or aneurysmal changes in the pathological descriptions was made in three[7,13,23] of the five without hypertension during the clinical course. In one case[30] with bilateral renal infarction there was listed but the initial admission blood pressure, of 140/80, one week after onset of the illness and one month before death. The other case[18] was normotensive during the last five weeks of illness, with old and recent renal infarcts revealed at necropsy. Including this case, 10[8,10-12,15,21,24-26] of the 16 with hypertension were noted to have renal infarcts at necropsy. It is reasonable to as-

sume that ischemia of adjacent renal tissue results from intrarenal aneurysmal formation. Such aneurysms were noted in four [7,13,14,20] of the other six pathological specimens. If this assumption is justified, this series then provides further evidence for the relationship between renal involvement in the disease, particularly with ischemic changes, and the development of hypertension.

As to whether the formation of a perirenal hematoma in the course of polyarteritis indicates a particularly fulminating form of the disease, there is noted in this series a range in duration of illness from 14 days [4] to about one and one-half years,[12] with an average of approximately four months. Rolnick's case [17] was living and well two months after nephrectomy for perirenal hematoma, which appeared 15 days after the onset of the illness. The case reported by Fort [22] lived for at least a year after the development of a perirenal hematoma. For comparison, 50% of 99 patients with polyarteritis in Rose and Spencer's study, excluding those treated with steroids, died in the first three months of illness. Furthermore, Diaz-Rivera and Miller [36] observed the average duration of life to be 50 days in six patients suffering from what they termed a "rapidly progressing form." It is difficult to assess and compare accurately these figures and those of other series because of the variability in properly interpreting time of onset of symptoms.

It is noteworthy that of the 25 cases of perirenal hematoma ensuing from polyarteritis nodosa 3 were bilateral. But for the rapid demise of most patients following the hematoma formation, perhaps more cases would have developed an additional episode of rupture through the renal substance of a diseased vessel. In all the cases in which necropsy was performed, both kidneys were found to be involved with the disease process.

Summary

An additional case of perirenal hematoma resulting from polyarteritis nodosa is reported, and observations, intended to be more provocative than conclusive, are made in connection with 23 other cases which have thus far appeared in the literature. Evidence is suggested supporting further the opinion that renal involvement is responsible for the hypertension frequently occurring as a manifestation of the disease.

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Psychodynamic Factors in Munchausen's Syndrome

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The term "Munchausen's syndrome" was applied by Asher [1] to describe a type of bizarre behavior, manifested by recurrent episodes of apparently feigned organic illness or factitious bleeding often associated with multiple surgical scars upon the abdomen, an evasive manner, and a fantastic personal history replete with amazing adventures and extraordinary achievements. Patients with this behavior have been called "peregrinating problem patients" by Chapman [2] because they travel from hospital to hospital causing consternation to the staff. Relatively little has been learned about the syndrome since Asher's report in 1951, and there is a notable lack of published data on possible psychodynamic factors. This is apparently a result of the recalcitrant nature of these patients.

The present report describes a patient who displayed the characteristics of Munchausen's syndrome and whose life history provided a basis for an understanding of possible causative factors.

Report of Case

The patient was a 34-year-old white man who appeared at the emergency room of the University of Oklahoma Hospital complaining of severe, cramping abdominal pain, which began suddenly a few hours earlier as he was watching television. He said that he had been hospitalized before for the pain. The surgical resident who first examined him described a well-nourished, well-developed man who appeared to be in severe pain. However, the pain seemed to decrease if his attention were focused elsewhere. The physical examination yielded little information other than five or six surgical scars upon the abdomen and diffuse, inconsistent abdominal tenderness. The patient was admitted to the hospital for evaluation. While on the ward, he continually demanded analgesics. His manner was withdrawn, and he appeared angry but created no disturbances. Except for a persistent leukocytosis of 14,000, with a normal differential count, the laboratory data (including hemoglobin, urinalysis, urinary porphobilinogen, and x-rays of the abdomen) were unremarkable. The patient readily agreed to any procedure, including any surgery the doctors might deem necessary. Psychiatric evaluation yielded a preliminary differential diagnosis of psychopathic personality or schizophrenia. The patient refused further psychiatric evaluation and was outraged that "The doctors think I'm crazy." He finally agreed to attempt the Minnesota Multiphasic Personality Inventory, but the score on the F (malingering) scale was so high the remainder of the pattern could not be evaluated.

Patient's Life History as Obtained from his Mother and Brother.—The patient was born in a small town in southeastern Oklahoma, the sixth of eight children in a laboring-class family. His infancy was unremarkable, with apparently normal delivery and development. At the age of 2 years, he suddenly had severe convulsions after having allegedly eaten two old pecans. He recovered uneventfully, and the convulsions never recurred. Nevertheless, from this time on, his family regarded the child as sickly. His parents let him do as he liked, in the hope that the convulsions would not return. His cruel and irascible father in particular indulged him, whereas before he had been very harsh in his treatment of the boy. When the child was 4 years old his mother left her husband, no longer able to endure his cruelty. She went to work in order to provide for the family but blamed herself for being unable to care for the children adequately. The boy entered school at the age of 6 years, and at 13 he was still in the third grade. He preferred the company of much younger, even preschool children or much older people who, his mother said, gave him a feeling of importance. She finally placed him in a special state school for retarded children at the age of 13 but withdrew him after a year and a half, having visited him only once during the whole period. Upon his return home, since there was no further effort at schooling, the boy became accustomed to passing his day by following an ambulance to a hospital near his home. The hospital director

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Resident in Medicine, University Hospitals, Oklahoma City (Capt. Rhoades), and Director, Brazos County Youth Development Service (Mr. Toland).

became friendly with him and invited him to help. At first, his tasks were simple, but ultimately he participated in surgical operations, obstetrical deliveries, and other procedures. Many times, when an emergency occurred, he would be asked to help.

His interest in excitement was not limited to his work at the hospital. He began to attend all fires in the vicinity, helping the firemen until the blaze was extinguished. According to his mother, "He never seemed happier than when holding a firehose on a blaze."

Drownings, too, were of great interest to him. Whenever he heard of a drowning, he went to the site of the tragedy, staying day and night until the body was recovered. He often traveled great distances to see drowned bodies recovered and at times participated in the recovery himself.

After one Oklahoma tornado, he worked for three days digging for bodies. He allegedly collapsed after recovering the 28th victim.

At age 30 years, he married a 19-year-old woman who had a 1-year-old son. He spent very little time with her, however, and, according to his mother and brother, the girl spent most of her time in barrooms. The patient, however, denied any domestic difficulties. He displayed no emotion while talking to doctors about his wife and refused to discuss his sexual relations. He and his wife had been apart six months prior to his last hospitalization. He was living with his mother and unmarried older brother, who owned a plumbing business, and he helped with the plumbing work when he was not traveling about to fires and drownings.

His mother and brother noted that he appeared to become restless at times when there was little excitement nearby. At such times, he began to appear at one hospital or another, doubled over, clasping his abdomen, groaning and apparently in great pain. His story was usually of being kicked in the abdomen by a horse or of receiving a blow to the abdomen in an automobile accident. Sometimes, he would contrive a fever by smoking and holding hot smoke in his mouth. Such behavior led to laparotomy on at least eight or nine occasions. Sometimes he left the hospital as early as two days after major surgery because the doctors refused him analgesics. On other occasions, he tore open large incisions so that he would have to be cared for again. He entered many hospitals in Oklahoma and Texas, usually a new one each time. Such behavior became much more frequent after the death of his doctor friend and the closing of the local hospital.

Two or three times, when he was being prepared for surgery, his brother arrived and suggested that nothing was wrong with the patient. Thereupon, the groaning patient would literally arise from the operating table and accompany his brother home. The brother seemed to share the patient's enjoyment of the startled discomfiture of the doctors and nurses. As the brother stated, on other occasions he actually precipitated the patient's admission to the hospital by finding fault with his work in the plumbing shop. He felt that the operations reflected a need for attention.

Comment

The history of this patient yields information about important psychodynamic factors in this particular case of Munchausen's syndrome. The patient was born into an emotionally hostile atmosphere, with a harsh and brutal father. The occurrence of convulsions suddenly brought him indulgence and immunity from abuse. After the separation of his parents, his mother rejected him by placing him in a school for mental defectives and failing to visit him. After his return home, he was met with equal indifference. His life took on meaning and importance only through his doctor friend and through his impressively important duties in the hospital. It is not difficult to understand his growing hunger for emergencies of all sorts. In his mind, this had come to mean acceptance and importance, if not love. His heterosexual relationships were inadequate, and other channels of personality development were pitifully shallow. When his brother, to whom he was closely drawn after the death of their father, rejected him by criticizing his work, the patient had only the hospital scene to turn to for emotional gratification. It was the same brother who, by his interest and comradeship, would, at times, save him from unnecessary surgery. Except for his brother's support, he had few satisfactions other than being a "hero" at fires and drownings. His adaptation to life included defective judgment, failure to pursue a consistent goal-directed course, pathological lying, and a failure to admit guilt, with an inclination to impose on and blame others. This type of basic maladjustment to the environment is conventionally characterized as psychopathic personality. The patient never exhibited any psychotic behavior, delusional ideas, or

hallucinations. Neither did he exhibit neurotic symptoms arising from inner conflicts.

Munchausen's syndrome becomes less mysterious when a complete history can be obtained. The means this patient adopted for achieving emotional satisfaction are not beyond comprehension in the light of information about his early personal development and traumatic family life. The patient's pathological behavior is seen to be predicated upon a need to achieve satisfactions obtainable by no other means.

Summary and Conclusion

A case of Munchausen's syndrome is presented in which it was possible to study the life history and (to a degree) the emotional development of the patient. In view of these data, the bizarre behavior of the patient takes on meaning and fits into a reasonable psychodynamic formulation. In this particular patient, we have seen a person who very early developed difficulty in establishing rapport with his environment. This was followed by a series of incidents, each of which, in itself, was not unusual, but which, in this patient, added up to the bizarre behavior. It should not be presumed that these same mechanisms are operative in all cases of Munchausen's syndrome. Further study of patients with this syndrome is needed before drawing definite conclusions regarding the etiology.

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Hyperparathyroidism, with Pseudoerosion of the Sella Turcica

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The roentgenographic findings in osteitis fibrosa cystica are well known. These advanced osseous changes due to demineralization and cyst formation are easily recognized in the roentgenograms of the extremities, spine, and skull. We recently observed one such case, which manifested an almost complete lack of visualization of the sella turcica associated with hyperparathyroidism. The disturbance was so marked that an intrasellar tumor was suspected. Although marked demineralization of the skull may occur, the outline of the sella turcica usually is preserved.

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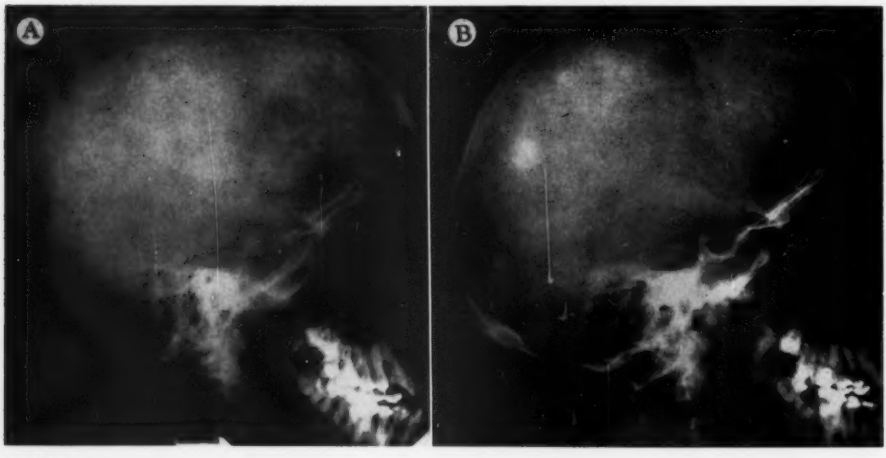
Report of Case

A 16-year-old girl fell from her bicycle in June, 1953, and fractured the right tibia. Roentgenograms at another hospital revealed a fracture through a cystic lesion. She was placed in a plaster cast for six months. Interval roentgenograms revealed progressive enlargement of the cyst, although union of the fracture occurred. In June, 1954, she was readmitted to the same hospital and a skeletal survey revealed multiple "cystic lesions" in the clavicle, humeri, ilium, and left tibia. The hemoglobin was 10 gm. Renal function was compromised in that the urine concentrated poorly and only small amounts of P. S. P. were excreted. The blood urea nitrogen was normal. Serum calcium ranged from 7.2 to 11.2 mg. %; serum phosphorus ranged from 3.6 to 4.8 mg. %. The serum phosphatase was 19 Bodansky units. Urine calcium excretion was 324 mg. in 24 hours. A diagnosis of primary renal disease with secondary hyperparathyroidism was postulated, and she was discharged on a high calcium and phosphorus diet.

Fig. 1.—*A*, preoperative appearance of the skull, showing "ground glass" appearance of calvaria, cystic changes, and apparent enlargement and erosion of the sella turcica. *B*, seven months after removal of a parathyroid adenoma. The sella is normal and the bones have remineralized. A 10 kv. decrease in technique was used in *A* because of marked demineralization.

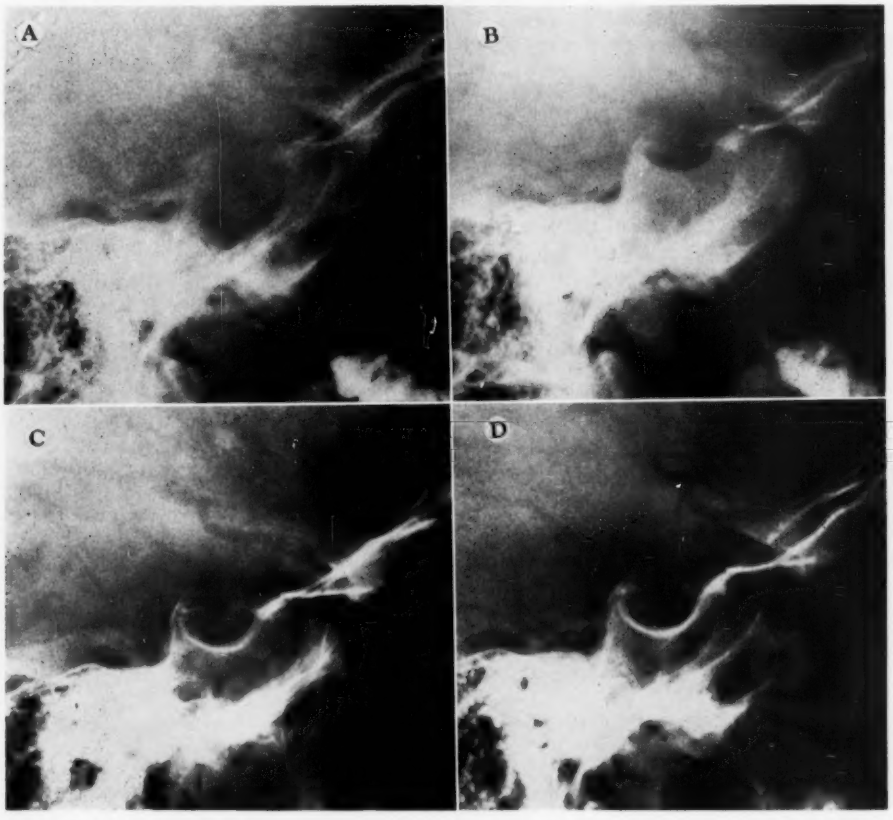


Following this she was able to walk only with the aid of a long leg brace and a crutch. In February, 1955, she became aware of a swelling in the region of that clavicle and mandible. Her appetite remained good, but she experienced occasional bouts of nausea. There was no polydypsia, but nocturia was present.

On April 15, 1955, she was admitted to the Hospital of the University of Pennsylvania for the first time. On examination she appeared thin and chronically ill. The mucous membranes were pale and the skin dry. Nontender masses over the right tibia, mandible, and left clavicle were very apparent. A small nodule was palpated in the left lateral aspect of the neck. Blood pressure was 120/80. Slit lamp examination revealed calcification in both conjunctiva and cornea; visual fields were full. Hemoglobin was 56%. BUN was normal, but the urine was poorly concentrated and the P. S. P. was excreted in limited amounts. Serum sodium, potassium, chloride, CO_2, PBI and total proteins were all within normal limits. Fasting blood sugar was 67 mg. %. Alkaline phosphatase was 28.7 Bodansky units; 17-ketosteroid excretion was 2.7 mg. in 24 hours, and there was an inadequate fall of circulating eosinophils following a four-hour intravenous infusion of corticotropin (ACTH).

Roentgenograms revealed the following findings: Skeletal survey showed a diffuse osteoporosis; multiple radiolucent defects were noted in the ribs, clavicle, and 2d cervical vertebra, with compression of the 12th dorsal vertebra. Examination of the skull demonstrated a diffuse demineralization of the bones of the calvaria, with a "ground glass" appearance (Fig. 1*A*). There was a cystic lesion in the left frontoparietal region. The sella turcica could not be seen, and it was thought that a pituitary adenoma with marked enlargement and erosion might be present (Fig. 2*A*). The lamina

Fig. 2.—*A*, preoperative appearance of sella turcica. *B*, six weeks after removal of parathyroid adenoma. The more rapid mineralization of the sella as compared to the other bones produces the very dense appearance. *C*, three months postoperative. *D*, seven months postoperative.



dura was not visualized. An intravenous urogram revealed nephrocalcinosis but good dye excretion. Upper gastrointestinal study was normal. Examination of the chest revealed normal lung fields, but fluoroscopically there was displacement of the trachea and cervical esophagus to the right. This was thought to be due to a mass in the left lower lobe of the thyroid or left parathyroid.

On April 27, 1955, a parathyroid adenoma was removed from the left side of the neck. The other parathyroids were normal. Twenty-four hours later the patient experienced mild perioral paresthesia which was quickly and completely relieved by intravenous calcium gluconate.

On May 7, 1955, the serum calcium was 8.3 mg. % and serum phosphorus 2.4 mg. %. She was discharged on a diet high in calcium and iron.

The patient did extremely well in the ensuing two months, and the roentgenograms of the bones revealed a rapid return to normal, although there were some residual changes at the sites of the cysts. It became apparent that the bony structures forming the sella turcica could not be seen previously because of marked demineralization, rather than erosion from a tumor. These bones rapidly remineralized and actually became relatively dense, when compared with the other bones of the calvarium (Fig. 2).

Comment

We were particularly interested in the appearance of the sella turcica when the patient was first admitted to our hospital (Fig. 2*A*). The bony wall of the sella could not be visualized, and we felt that it was enlarged.

We had in mind the syndrome of adenomas simultaneously occurring in the anterior pituitary, the parathyroids, and the islets cells of the pancreas, either in all or in any two of these organs.[1]

The parathyroid adenomas are characteristically multiple in these cases, as are the islet-cell adenomas. The pituitary adenomas are either esoinophilic or chromophobic. It has been emphasized that in the early stages one endocrine tumor may dominate the physiological manifestations, even though anatomically all three glands are abnormal. With progression, a complicated mosaic of endocrine derangements may appear. Such a complex clinicopathologic picture has been seen often enough that the possibility of mere coincidence probably can be dismissed.

In the case presented, the glucose tolerance and blood sugar were normal and the only suggestion of multiple adenomas was the appearance of the sella turcica. After removal of the parathyroid adenoma it rapidly became evident that the apparent erosion of the sella turcica was merely due to a marked demineralization of the bones forming the sella turcica (Fig. 2). In retrospect, an intrasellar lesion of the size we suspected should have produced some change in the visual fields, which was not present.

Summary

A case of hyperparathyroidism with osteitis fibrosa cystica is presented. Unusually poor visualization of the bones forming the sella turcica falsely suggested erosion due to an associated intrasellar tumor. The misleading appearance was due to a marked demineralization of the sella. Removal of a parathyroid adenoma permitted rapid remineralization of an otherwise normal sella turcica.

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Note on a Monstrous Finger

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In our sometimes apathetic acceptance of nature we rarely wonder at the marvelous symmetry of man. This he has in common with most highly advanced creatures. We take it for granted that as we grow our right and left sides will remain roughly symmetrical. Most persons start and stop growing at the appointed time. Only when growth fails and results in various kinds of dwarfism or exceeds its regular confines in gigantism and acromegaly do we notice nature's mistakes. Then we wonder what are the governors, the starters and the stoppers of growth? More freakish and rare than dwarfs or giants are examples of local gigantism. These are not well understood either. Even the common clubbing of the fingers and osteoarthropathy, acquired reversible forms of modest localized overgrowth, are comprehended only in part. Though we know something of mechanisms, of hormones, and of the role of the circulation of blood, we are scarcely in a position to ask the really searching questions which might light up this dark ground of ignorance.

Our purpose is to record an example of local gigantism in a man with a monstrous finger. Even though we do not have a clear understanding of the problems of growth which it illustrates, such an example may stimulate thought and speculations which lead to work which might help clarify such complex puzzles. Understanding this one anomaly certainly would help us comprehend many phenomena of growth and development.

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From the Department of Internal Medicine and the University Hospitals of the State University of Iowa College of Medicine.

Report of Case

The patient, a 53-year-old white man, a bartender, was admitted to the University Hospitals for the first time on July 16, 1958, with a provisional diagnosis of bronchogenic carcinoma. Apparently he had been well until three months before admission. Then he noticed fatigue and mild dyspnea while exerting himself. He was able to continue his work as bartender until three weeks before admission, when he became severely dyspneic. He was unable to walk more than a few steps before getting completely out of breath, and he became greatly fatigued by the slightest effort. Vague pains in the left side of the chest were increased by inspiration and relieved by lying on his left side. His chronic cough had grown worse and was productive of about a pint of yellow tenacious sputum every day. There were no fever, hemoptysis, chills or night sweats. He had lost about 10 lb.

The patient was first noted to have localized gigantism at birth, when his mother noticed that the middle finger of the left hand was much bigger than the middle finger of the right hand. The fourth finger of the left hand was slightly enlarged. The growth rate of these fingers approximated that of the other fingers, so that the discrepancy in size persisted throughout the period of growth. The finger functioned well and in his work as a bartender gave him an uncanny leverage with bottles and glasses. There had been no similar deformity in any members of his family, including siblings, parents, grandparents, uncles, aunts, and cousins. There was no history of acromegaly. The patient was of average size for his family.

The physical examination revealed a well-developed, malnourished, white man, chronically ill and dyspneic. He was 5 ft. 8 in. tall and weighed 128 lb. The musculature and skeletal system were normally proportioned, with the exception of the deformed finger. The second finger of the left hand was 10 cm. in length, with a circumference of 7 cm. The third finger was 18.5 cm. long, with circumference of 11 cm. The fourth finger was 13 cm. in length, with a circumference of 8 cm. (Figs. 1-4). The blood pressure was 110/64 mm. Hg; the pulse rate 94 and the respirations 44 per minute. The skin was warm and moist, with cyanosis of the lips and nail beds. There were no palpable lymph nodes. The trachea was deviated to

Fig. 1.—Appearance of the outstretched hand, revealing the enormous middle finger, which, except for its great size, seems to be perfect. Slight enlargement and bending of the ring finger is apparent.

the right but the thyroid was not enlarged. The anteroposterior diameter of the chest was increased. The left thoracic excursion was reduced. The entire left side of the chest was dull on percussion. Breath sounds and fremitus were diminished. There was an area of egophony over the upper left lobe. No whispered pectoriloquy was noted. There were a few fine rales at the base of the right lung posteriorly. The breath sounds were slightly distant on the right. The cardiac border was not obscured. The right ventricle was slightly overaccessible. There was a sinus rhythm and a Grade 2 apical systolic murmur. The abdomen was normal.

X-rays of the left hand revealed the bones and joints to appear normal as were the soft tissues, with the exception of the disproportion in size (Fig. 4). This was interpreted as primary localized gigantism rather than secondary gigantism.

Urinalysis and hemoglobin were normal. The chest film showed massive left pleural effusion with shift of the mediastinum to the right. Thoracenteses yielded serosanguineous fluid in which malignant cells were found.

The patient's course in the hospital was one of progressive worsening. He died after a month. We could not obtain permission for an autopsy or even get permission to dissect the finger.

Comment

It is not our purpose to review all medical reports of localized gigantism. We shall confine our discussion to some major problems and speculations. Harris and Wright [13] have summarized the earlier experimental efforts to produce regional overgrowth by removal of parts of the sympathetic vasoconstrictor apparatus. Claude Bernard,[1] in 1867, observed no change in the size of the ears of rabbits or cats after he had removed the superior cervical ganglion. Bidder,[2] in 1874, was the first worker to observe an increase in size as well as temperature of a rabbit's ear after removing 1.5 cm. of the cervical sympathetic trunk. Harris and Wright had many negative results but did observe a readily measured increase in the

Fig. 2.—Comparison of the right and left hands, dorsal aspect.

Fig. 3.—Comparison of the right and left hands, palmar aspect.

growth of the ear of the sympathectomized side in three of nine rabbits.

Localized gigantism has been recognized as a freak of nature from ancient times. In paintings, sculpture, and old writings there are records of freaks and deformities. Gould and Pyle, who removed the topic from the leer of the side show into the big tent of respectable medicine, have in their collection of monstrosities examples of almost unbelievable localized gigantism parading in their picture gallery of horrors.

Localized gigantism occurs in at least three forms. The first, Parkes Weber [22] has called hemangiectatic hypertrophy. Ordinarily, it affects either a leg or an arm. Rarely, it affects only a portion of a limb, and still more rarely, only one finger. It is a dysplastic state of blood vessels associated with innumerable arteriovenous connections or a few smaller ones producing a large angioma with a great increase in the volume of blood flow. Presumably underlying bone has an exuberant growth be-

Fig. 4.—Radiographs of the left hand in the anteroposterior and lateral views. Note that the bony enlargement is confined to the phalanges and does not involve the metacarpals, and so the palm of the left hand was very little different from that of the right.

cause of forced irrigation with blood. This inborn fault of structure is merely one form of the larger pattern of disease in which the skin is involved in angiomatous and telangiectatic changes with widespread deformity of the underlying vascular structures with angiomas, hamartomas, atrophy, deformed structure, and disordered function of the underlying tissue. The Sturge-Weber-Kalischer syndrome is the same sort of inborn dysplastic angiectasis affecting the face, scalp, and underlying portions of the brain.

A second form of localized gigantism occurs with clubbing of one digit. I have had under observation for many years a patient who developed clubbing of the thumb after a sympathectomy on the same side.

The third variety of localized overgrowth of an extremity or a finger is associated with extensive underlying lymphangiectasis. The lymph spaces are enormously increased in size and capacity. Usually there are many ramifying channels. Often they have major connections with blood vessels.

For many years it has been known that forms of von Recklinghausen's neurofibromatosis may be associated with asymmetries, hypertrophies, and deformities of limbs or individual digits. According to Campbell,[6] the first such cases seem to have been reported by Broca, in 1859. When Campbell reviewed the literature in 1923 he was able to find 70 case reports. A number of additional ones were added by Brooks and Lehman.[5] Winestine[23] made an extensive review of the problem, including the gigantism of visceral organs in mesenteric neurofibromatosis and segmental neurofibromas with segmental visceral gigantism. He cited much of the pertinent literature up to that time. In discussing facial hemihypertrophy, Brain[4] described a 26-year-old man with spinal deformity which had progressed since the age of 2 years along with hemihypertrophy of the right side of the head and deformity of the spine. In addition to the lopsided head, there was hypertrophy of the skin and subcutaneous tissue blocking the right palpebral fissure and the external auditory canal, along with hypertrophy of the gums on the right and enlargement of the papillae of the right side of the tongue. The bones of the right arm were longer than those of the left, and neurofibromas were found above the right zygoma. In 1941, Moore[17] summarized the prevailing views and discussed the complications of neurofibromatosis under the heading of endocrine disorders, mental changes, malignant transformation, and skeletal changes, which included scoliosis, abnormalities in bone growth and structure, and congenital pseudoarthroses in children, illustrating these findings in four case reports. After a discussion of various theories, he concluded that the most plausible explanation was that there was faulty control of growth rather than faulty growth per se, since there was undergrowth of some parts as well as overgrowth of others. He found that localized hypertrophy was associated with neurofibromatosis often enough in a segmental relationship to suggest a cause and effect connection. Hypertrophy did not occur as pure overgrowth but was an example of uncontrolled growth with reduction as well as augmentation. Endarteritis in the bone was thought possibly to have a bearing on the problem. Inglis,[14,15] in several papers, has emphasized the relationship of neurofibromatosis to change in bone growth and alteration in bone structure. Though he introduced some new terminology into the discussion of factors governing growth and carrying it to an appropriate end, he was not able to determine through what mechanism these obvious but still poorly understood forces might operate. Inglis believed that there are intrinsic and extrinsic factors which determine and control growth and development. He concluded that localized gigantism may be caused by (1) an abnormality in nerve supply, (2) an abnormality in blood supply, and (3) an abnormality in humoral control.

Except for the cancer of which our patient died, we could not demonstrate any

other abnormality. The circulation, skin temperature, or structure of the underlying bone were normal. There was no hereditary factor, hydrocephalus, mental disease, epilepsy, malignant transformation of the structure, cutaneous pigmentation, or any apparent hemangiomatosis, and there were certainly no signs of congenital pseudoarthroses, spinal curvature, absence of bones, or altered size of other bones. Thus if neurofibromatosis occurred it affected only the one area for only one finger was involved. We could not discover any sign of increased blood supply. We did not study lymph drainage and therefore do not know whether a lymphangioma or a lymph hemangioma might have been present. Thus, we are totally in the dark about why, in this particular patient, a digit, which was already abnormally large at birth, continued throughout growth to maintain its relative disproportion and to present a grotesque but not a crippling deformity.

Summary and Conclusions

We have reported a patient with localized gigantism of a finger. As far as our observations went, there was no indication of neurofibromatosis, angiomatosis, or any other vascular or lymphatic anomaly to explain this prodigy. We suggest that while various mechanisms we have discussed may account for many such anomalies of growth, there are others for which we have no present explanation.

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Treatment in Internal Medicine

The Management of Parkinson's Disease

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I. Historical Review

In 1817, James Parkinson [1] described six cases of the condition which now bears his name. These were all men with a disease state he characterized by tremor, loss of finger and arm dexterity, propulsion, festination and falling, insomnia, constipation, and dorsal kyphosis. Finally, there came on aphonia, dysphagia, and incontinence. From reading the text, it is apparent that these cases had generalized slowness of movement and marked dependence on others for the ordinary tasks such as eating, dressing, and walking. Rigidity is curiously not mentioned, but it is fair to say that it must have been present in order that the other symptoms might appear. The following quotation will remind present-day students of the acuity of his observations:

. . . . [p. 3] The first symptoms perceived are, a slight sense of weakness with a proneness to trembling in some particular part; sometimes in the head but most commonly in one of the hands and arms. . . . [p. 4] After a few more months the patient is found to be less strict than usual in preserving an upright posture. . . . Sometime after the appearance of this symptom, and during its slow increase, one of the legs is discovered slightly to tremble and is also found to suffer fatigue sooner than the leg of the other side. . . . As the disease proceeds writing and nice manipulation of the hands are accomplished with considerable difficulty. . . . [p. 5] The submission of the limbs to the directions of the will can hardly ever be obtained in the performance of the most ordinary offices of life. . . .

Parkinson noted some gross abnormalities in and about the brain stem in two autopsied cases to which he had access and therefore proposed (without microscopic histology) a theory of brain stem and medullary pathology for the condition. As far as we can determine, cases of Parkinson's disease frankly attributable to encephalitis were not described until after the encephalitis lethargica epidemic of 1918. These cases had obvious differences from Parkinson's original six men. In the past 50 years, other causes have been implicated as well, as we will consider below.

The first really useful medication for the condition was scopolamine advocated by Charcot [2] in his lectures published in 1892. Since then, there has been a series of claims for the efficacy of diet, climate, sedatives, spa therapy, tonics, periods of long rest, and various regimens of exercises. Henry Von Witzleben's monograph (1942)[3] represents an astounding number of these, including the extravagant and mystic claims for bulgarian belladonna root as proposed by Ivan Raeff.[4] One striking thing is that the older claims appear to differ but little from the claims put forth by advocates of current medical and surgical methods. It is essential, therefore, to assess the present status of this condition in order to appreciate properly the problems and limitations of current methods of treatment.

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II. Pathology

Pathologists have given careful attention to the features of this condition during this half century, and there exist many very complete monographs on the histopathology. Excellent summaries of these are provided in the recent discussions of Denny-Brown (1954),[5] Abner Wolf (1954),[6] and Greenfield (1955).[7] These are based on the important work of Foix and Nicolesco (1925),[8] Bielschowsky (1922),[9] Hassler (1938),[10] and Benda and Cobb (1942).[11] There is generally agreement that nerve cells are damaged or absent, especially in the substantia nigra and less so in the globus pallidus and lower down in the locus caeruleus and dorsal vagal nucleus of the medulla; the cerebral cortex, too, may be involved in some. Pigmentation of the substantia nigra is usually lost or strikingly diminished. There are, at times, "amyloid" bodies in some cells of the substantia nigra and brain stem, as first noted by Lewy.[12] Neurofibrillary change, scarring, and gliosis are common with some lacunar development. Yet some pathologists, such as Oseki (1924),[13] maintain that no change exists which is different from that ordinarily encountered in the senium. It is worth while to remember that Roth and Bebin (1958)[14] describe 34 cases of basal ganglion gliomas, of which 7 had signs of Parkinsonism, and that Hardy and Stevenson (1957)[15] note a case of a syrinx in the substantia nigra with Parkinsonism. However, Greenfield concluded in 1955 that there had been no new recent developments in the pathological understanding of Parkinson's syndrome and that new light upon the condition would have to come from some other discipline than neuropathology.

From our clinical viewpoint it is clear that a few of our cases were related to indubitable encephalitis lethargica. We see no reason to question the pathological opinion that arteriosclerosis itself is not a causal factor in spite of the arguments mustered by Critchley (1929).[16] Basal ganglion tumors and similar abnormalities are rarities; we have no such recognized cases among more than 800 we have seen at our clinic. Arguments advanced by Schwab, Doshay, Garland, Bradshaw, Garvey, and Crawford (1956)[17] imply there may be some relation to an event such as the influenza epidemic from 1917-1926, even when encephalitis cannot be recalled by the patient. Yet, at best, this evidence is indirect. Over half of our large series do recall that they had influenza during the epidemic, but many of these had such mild forms that this past history satisfies few critics. We feel that the clinician is forced to regard the majority of his cases of Parkinson's disease primarily as idiopathic at the present time. A metabolic factor, as Brock (1956)[18] suggested, might very conceivably afford an explanation, but time will have to disclose it.

It is probably fair to say that this condition is a "definite morbid entity," as a disease is defined by Stedman, because there is a certain consistency about the pathological findings, clinical signs, and symptoms. However, inasmuch as the clinical picture is variable, and causative factors poorly understood, Parkinson's disease must now be conceived of as a frustratingly nebulous clinical concept.

III. Neurophysiology

Neurophysiology has contributed some interesting and pertinent observations. Varying qualities of tremor, a cardinal phenomenon in this disorder, have been produced by specific brain stem lesions in animals. Carpenter, Whittier, and Mettler (1950)[19] have noted that, though tremor in monkeys has arisen with lesions of the superior cerebellar peduncles, the brachium conjunctivum, and the rubrospinal tract, this tremor usually has more or less the character of the "action" or "intention" tremor of cerebellar disorders. For instance, Carey and Dejong's monkeys (1954)[20] with red nucleus lesions had such a fine action tremor. Ward, McCulloch, and Magoun (1948)[21] have observed a more pertinent resting alternating tremor with lesions of the dorso-

lateral and ventrolateral mesencephalic and pontine tegmentum. Jenckner and Ward (1953)[22] presented a "rhythmic alternating peripheral movement" in monkeys, induced by high-frequency stimulation of the medial reticular formation of the brain stem from rostral to the red nucleus down to the level of the pyramidal decussation. This tremor was abolished by drugs, especially scopolamine and diethazine (Diparcol). These authors titrated the effectiveness of a number of anti-Parkinson drugs and proposed the theory that nerve cells in the area of the brain stem might be denervated in Parkinson's disease and thus hypersensitive to acetylcholine. All of the currently used medicines effective in Parkinson's disease are somewhat anticholinergic.

Schreiner et al. (1958)[23] produced very convincing motion pictures of monkeys with lesions placed in the rostral brain stem reticular formation. Motion pictures of these monkeys two months later showed very convincing resting tremor that disappeared with movement, increased resistance to passive muscle stretching with demonstrable cogwheel phenomenon, poverty of spontaneous movement, lack of facial expression, some ataxia, and a tendency to remain in a fixed position for long periods. The resemblance to Parkinson's disease was certainly more striking than some of the previously mentioned specimens. There was adequate microscopic confirmation of where the lesions were placed. It is to be noted that in this report only 6 of 15 animals were in the group showing Parkinson-like symptoms. This is an indication of the difficulty in this type of research.

Rigidity is less easy to reproduce in the experimental animal. Decerebrate rigidity, as Sherrington's classic work[24] so clearly showed, occurs with transections of the brain stem from the level of the red nucleus down to the level of the superior border of the vestibular nucleus. It is featured by powerful extensor rigidity of all limbs, slight opisthotonos, and preponderant rigidity in the antigravity muscles. Decorticate rigidity, another familiar entity, ensues when the transection is high in the midbrain. It is more complex, with variations caused by posture and by the influence of labyrinthine reflexes. In primates generally this is a flexion rigidity of the arms with extensor rigidity of the legs. Neither of these conditions is very much like the plastic sort of resistance to movement in Parkinson's disease, where there is emphasis on rigidity of the anterior truncal muscles (producing the dorsal kyphosis) and the muscles of the arms.

In decerebrate rigidity, severance of dorsal spinal roots will abolish it segmentally. Ward (1947)[25] has shown that decerebrate rigidity is also facilitated by lesions superiorly in the lateral reticular formation and inhibited by those in the central bulbar reticular formation. Further physiological details concerning any sort of rigidity are few indeed.

There is, however, new knowledge of the muscle contractile spindle, a specialized muscle fiber from the small "γ" motor nerve cells in the anterior horn in the spinal cord. As Granit[26] has summarized, the spindle fiber subserves an internal stablizing function for its muscle, allowing motor discharge to the principal "α" contractile fibers from the large "α" nerve cells in the anterior horn of the spinal cord. These are regulated directly by a single reflex from the sensory response to the contraction itself via the tension in the spindle. This then is a true biological feed-back mechanism, called by Granit the "γ loop." Further, he and his co-workers have shown that this spindle system is itself regulated by higher centers. For example, stimulation of the contralateral internal capsule will inhibit γ-discharge and that of the contralateral inferior colliculus will increase it. Pollock and Davis' "anemic decerebration" preparations showed rigidity and inhibition of γ-discharge. On the other hand, decerebrate rigidity is associated with intense γ-discharge and dependent on it. Cutting the posterior roots and interrupting γ-input abolished the rigidity in the segment served by the roots concerned.

IV. Clinical Nature

With a condition of obscure causes, of variable pathological background, and physiologically far from clear, the clinician is forced to review his own clinical observations carefully in order to plan the medical and possible surgical therapies now offered.

Parkinson himself realized that, though tremor was an obvious and dramatic feature of his condition, there were many other sides to it, all of equal seriousness. We suggest a practical classification of these symptoms as follows:

In order to prevent confusion with other beginning alphabetical values and schema we have arbitrarily taken X, Y, and Z as the three letters representing the most prominent three classes of symptoms. Each will include a number of subgroups indicated by numerals. Since Parkinson's disease is chiefly a disturbance on the motor side of the nervous system, we will call the extremities, including arms, legs, feet, hands, and fingers, "motor end-organs." These symptoms invariably show up first on one side of the body and may remain unilateral for years in some patients.

Group X therefore is made up of the following symptoms:

1. *Tremor.* The characteristic to-and-fro four-per-second tremor of rest.

2. *Rigidity.* On passive motion of a joint with the patient relaxed there is a plastic as well as a cogwheel type of resistance.

3. *Loss of fine finger dexterity.*

4. *Loss of learned, associated, or cooperative muscle movements,* such as arm swing with walking, extension of wrist with grip of flexors.

5. *Reduction or loss of reflex expressive facial muscle activity.* This accompanies voluntary activity of arms and legs on the involved side and is actually part of speech and attention.

6. *Unilateral, peculiar, and often minimal postural abnormalities.* These are often unknown to the patient, such as flexing wrist or elbow toward the body when seated.

In the Y-group we include more complex and usually bilateral motor difficulties involving *disorders* of the coordination and synchronization that are necessary for the continuation of several motor patterns at the same time, with semiautomatic control of rate, intensity, and modulation.

1. *Reduction of muscle amplitude,* such as "petit pas" (small stepped gait), micrographia, lips held too close in speech.

2. *Disorders in correct timing of muscle patterns,* such as the hurrying in walking (festination phenomenon) and the running of words together in speech.

3. *Loss of various postural and gait reflexes* (pulsion), spinal kyphosis, head flexion, and jaw opening.

4. *"Freezing"* into one muscle pattern with loss of release and ability to change to the next pattern.

5. *Akinesia.* An apparent complex of disinclination or difficulty in starting a movement and continuing it. Amplitude falls away as if in a tremendous fatigue curve.

6. *Kinesia paradoxa.* Ability to make sudden and rapid movements under extreme motivation with previously incompetent muscles.

7. *Dysarthria,* which is essentially involvement of speech with Y (1), (2), and (5) so volume loss makes the voice inaudible or loss of word changing gives stuttering-like repeats.

8. *Difficulties with ordinary reflex patterns,* such as spontaneous blinking of eyes (normal is 12 to 15 times a minute); automatic evacuation of pharyngeal saliva by swallowing; regular restless extremity movements, even when listening or reading, that aid muscles in keeping circulation in both directions, for example, in the dependent feet when seated.

The Z-group of symptoms is left for those that point to the spread of the Parkinson disease process to other areas of the brain than those dealing with motor activity.

1. *Specific cranial nerve involvement.* Spasms or crises, such as locking of eyes in upward gaze (oculogyric), severe blepharospasms, muscle spasms in jaw.

2. *Spread to autonomic centers,* such as oily skin, obesity, excessive sweating, severe constipation, incontinence, palpitation, and nonrenal and noncardiac hypertension. Also, insomnia and excessive somnolence.

3. *Involvement of higher brain centers,* with changes in personality, development of phobias, tics, habit spasms, memory losses, and tolerance and/or carelessness toward filth, odors, soiling. Finally, development of psychotic behavior, with hallucinations, delusions, and, finally, dementia and deterioration.

The first point that we would like to make in the consideration of the above is that

there is a great deal of variation in the prominence of the individual symptoms. It is rare indeed to see two cases exactly alike, and the various mixtures of these 17 groups provide an extraordinary variety of patterns. Instances of pure tremor confined to one or more extremities are well known. More often, cases of Parkinson's disease demonstrate principally peripheral tremor and rigidity. The X-group show as their chief symptoms rigidity and resting tremor, with loss of associated movements in varying amounts. They do not have impairment of memory, personality change, or dominant cranial nerve disturbances. They have little, if any, of the akinesia; indeed, they have excellent motor power in spite of the tremor and rigidity in their muscles. Their speech and swallowing are little affected, and psychological studies show that there is little, if any, intellectual impairment. Most of these have normal electroencephalograms. In spite of great difficulties due to loss of fine finger dexterity in the presence of rigidity and to the annoyance of tremor, they remain largely independent of help and assistance, even though it may take them two or three times as long to do an ordinary task, such as dressing themselves. Friends and intimates of such patients are astounded at their courage and perseverance and determination in carrying out their usual chores and tasks each day and overcoming the handicaps that their symptoms produce. This group should be kept in mind because it is with them that the most help and assistance in the management of the disease is possible.

However, the difficulties in Group Y are even more incapacitating. We would like to emphasize "akinesia," a reluctance to initiate movement, as a particularly important phenomenon. We have seen patients in whom tremor and rigidity were minimal and yet the features of Group Y proved devastating (Schwab, England, and Peterson, 1959).[27] Very early in the disease with this group of patients a very alarming and disturbing dependence emerges. Even when their rigidity is minimal and tremor absent they leave their jobs, become house-bound, and are increasingly unable to look after themselves. Help in dressing, eating, bathing, and even getting in and out of bed is required soon in their disease, and they may remain for long periods at a time incapacitated in one place in a room, apparently unable to extricate themselves from some uncomfortable position. Continual episodes of "freezing" occur, where they have to have help not only from their family but from passengers, for example, to get them from a bus and on to the curb. Although their hearing, vision, and other sensory apparatus seems perfectly intact, it is obvious that they are having considerable difficulty reacting to such stimuli. Speech and swallowing are frequently severely affected in this group of patients, and they may appear to be uncommunicative, indifferent, and severely obtunded. Usually, sooner or later, they take on Z-group signs and symptoms. Psychological testing of such patients reveals marked losses of an irregular type, and frequently the ordinary psychologist is so baffled with this picture that he regards them as largely demented and deteriorated. However, this is not always true, for under extreme stimulation these patients can suddenly make very apt and even profound comments about subjects with which they were familiar or bring forth a witty remark, indicating very concise comprehension of the conversation going on. For example, such patients can, if the house catches fire, leap from their invalid bed, run to an adjoining room, grab a child, and run down the stairs. After the event is finished, they will immediately revert to their invalid state. Electroencephalograms of such patients show diffuse slow waves, and an air study usually reveals dilation of the third ventricle and aqueduct. They are by far the most difficult to treat because they are often extremely sensitive to the solanaceous and sedative drugs.

V. Qualitative Measurements

Many clinical and laboratory efforts have been made to qualify and quantitate the

various abnormalities. These have included the elaborate rigidity tremor of Agate et al. (1956),[28] the tremor photographs of Campbell (1947),[29] the Purdue pegboard of Kaplan, Machover, and Rabiner (1954),[30] and the tremor recorder of Schwab and Prichard (1951).[31] Experience has taught those who have worked in the field that all measuring parameters of evaluation have serious limitations. Devices to record the abnormalities of muscles and muscle action suffer because the muscles are apparently a good way from the source of the disturbance in the basal ganglion region. Emotional variations in the Parkinsonian state are most disconcertingly difficult to control. It seems, therefore, important to keep mechanical recording devices very simple, since there is no present justification for elaborate apparatus to check on the clinical situation.

Schwab and England (1956),[32] in an initial medical survey of 26 selected patients who had surgical intervention by Dr. Irving Cooper, arranged with some satisfaction 10 categories of subjective and 10 of objective evaluation. (An almost identical set of criteria has been independently described by Shapiro, 1956.[33]) (See the subjective and objective evaluation sheet, Chart 1.)

Each of the 10 categories is scored from 0 to 10 as performance varies from none to perfect. The sum of the 10 scores yields a figure representing a rough percentage of normality. We have found that such scoring is a very convenient guide, a framework within which the examiner thinks in terms of the patient as a whole. We will admit at once that such scoring may vary somewhat according to the mood of the individual examiner and that of the patient. Any experienced clinician will appreciate the basic value of a detailed description of the patient's actual function in simple and clear terms.

We should like to make particular mention of six simple clinical tests which are very reproduceable and which require little or no equipment (Figs. 1 and 2).

1. The tracing of a 4 in. circle on paper with a pencil as rapidly as possible with each hand individually, 10 times. Both the trace time and the record of the 10 circles have value. The normal person can make such a 4 in. circle with a pencil in about three seconds, and the circles will be smooth, regular lines, running one over the other.

Name.

	SUBJECTIVE				OBJECTIVE			
	1953	1956 (Date worst)	1956 (Recent best)	(On new drugs) 1957	1956	1956 (Date worst)	1956 (Recent best) 1957
1. Clothes	7	5	8	1 Rt. Rig.	5	4.5	7
2. Toilet washing, shaving	6.5	5	8	2. Left Rig	6	6	8
3. Sleep Rest	8	5.5	8	3. Rt. tremor	5	4.5	8
4. Food	8	6	8	4 Left tremor	6	5.5	8
5. Indoors	8.5	6	8	5 Rt. swing Ass. Mov.	6	5	7.5
6. Outdoors	7	5.5	8	6 Left swing Ass. Mov.	7	6	7.5
7. Social	7	6	8.5	7 Rt. Ergo	6	5.5	8
8. Travel	8	6	8.5	8 Left Ergo	7	6	7
9. Occupation	7	5	7.5	9. Combined test	6	5	7
10. Morale	7	6	8	10 Gait, Post. Facies.	7	6	7
TOTAL	74	56	80.5	TOTAL	60	53	75

Score in percentage of normal values to nearest 10%

Normal	10	None	10
Good	8	Minus	8
Fair	6	1 plus	6
Poor	4	2 "	-
Trace	2	3 "	2
None	0	4 "	0

Chart 1

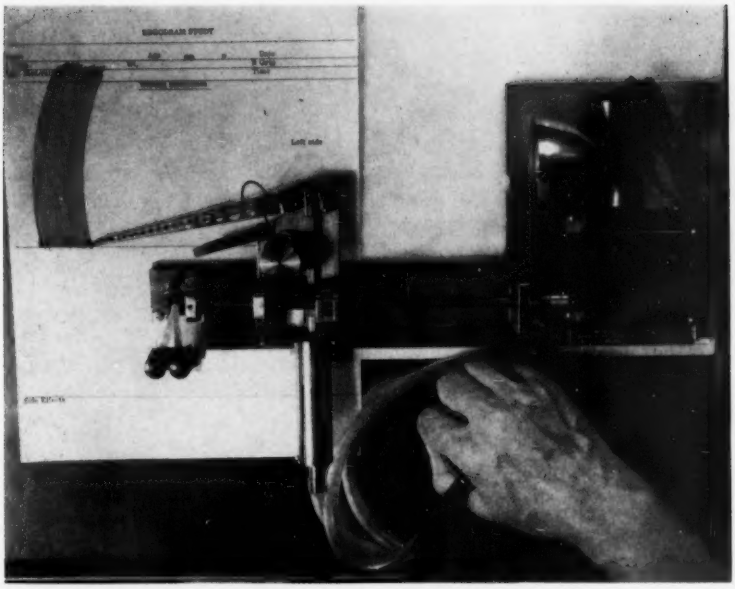
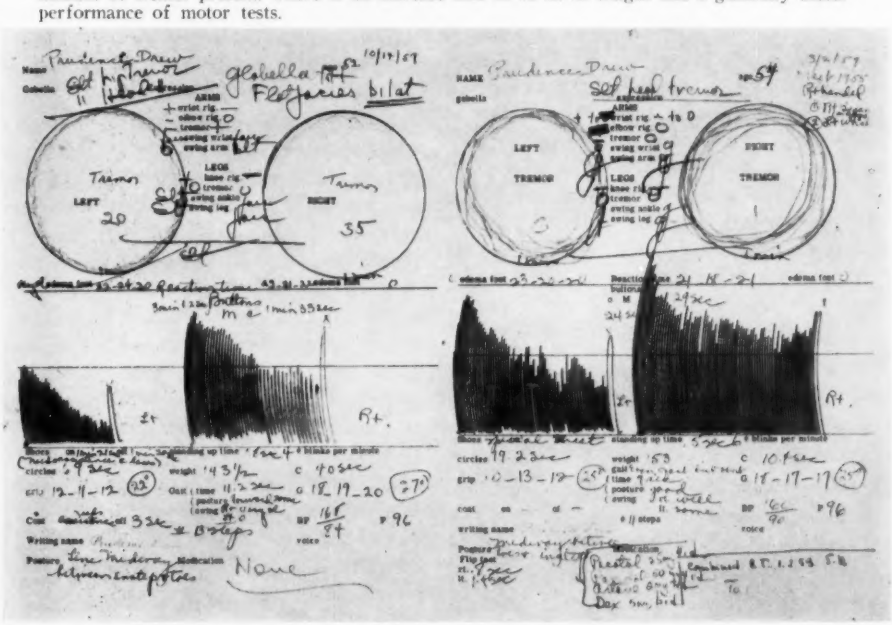


Fig. 1.—Detailed photograph of the bulb ergograph which we have used for many years. The bulb is in the patient's hand at the lower-right-hand corner. The bell, which is indicated by a revolution every second, is in the upper-right-hand corner and rings every second. The ergographic curve as it is written out shows in the upper-left-hand corner of the photograph.

Fig. 2.—A photograph of two work sheets on the same patient 18 months apart, indicating the number of objective measurements and tests employed. The unusually objective and consistent improvement in this particular case is shown by the tests and is due to the medication the patient was taking. The findings on the left side of the body are on the left side of the chart, and the right are on the right side of the chart. The tremor is indicated in units in each of the circles. The ergographs show the improvement in power in both sides that the medication produced. It should be noted that the neurological findings are not very significantly changed and that the most striking improvement is in the ergograph and in the amount of tremor present. There is an increase also in 10 lb. in weight and a generally faster performance of motor tests.



A Parkinson's patient, however, may take anywhere up to 25 seconds to do this, and there may be a strong tendency for the circles to get ever smaller as he goes along; the presence of tremor shows itself by irregular lines. We have found this a useful test because it shows clearly the difference between the worse and better sides and usually reflects any improvement in motor speed provided by therapy.

2. A simple specimen of handwriting, such as the signature or "It is a beautiful day today." This is always eloquent evidence.

3. The time required to walk 10 yd. as fast as possible (not running). A normal persons covers this distance in somewhere around five to six seconds, and the Parkinson's patient with his shuffling, slow gait may take two to four times this amount of time. During such a test of gait, the doctor or nurse can observe whether the arms are swinging in a normal way or flexed in a fixed position against the patient's side.

4. A record of repeated contractions against resistance of an air-filled rubber bulb by the hand, done at a rate of one grasp each second. Rapid loss of amplitude ("fatiguing") is often a feature in Parkinson's disease. The bulb ergograph * is a useful piece of equipment, but an Asepto syringe bulb attached to the mercury or aneroid blood pressure apparatus will do (Fig. 1).

5. The time required to button and unbutton a a test set of buttons and buttonholes on two pieces of cloth.

6. The time required to take shoes off and put them on, to tie shoelaces, to put on and take off a jacket or other article of everyday clothing.

It is our present feeling that the use of a selected number of these tests will be a useful addition to the clinical impression or note of amount of tremor and rigidity at each visit. In research work we have been impressed by the dramatic usefulness of cinematographic records, which have been so ably employed by Dr. Irving S. Cooper to demonstrate the effectiveness of his surgical intervention.

VI. General Medical Treatment

There has been a feeling, prevalent among many doctors in the past, and it still is held by some, that a patient with Parkinson's disease ought not to be told either the name of the condition or its nature. This is justified on the supposition that such knowledge could only add to the patient's already heavy burden. We wonder whether such withholding is really motivated by true kindness and sympathy on the part of the physician. It appears to us often to represent a medical reluctance, combined with ineptitude, in conveying the truth to the patient in a manner which will not upset him emotionally. The truth will clear misapprehensions and afford better understanding to the patient. We feel strongly that the patient ought to appreciate that, in the fashion of diabetes, peptic ulcer, et cetera, his condition will probably always be present, that it may worsen, that some drugs may be of suppressive value, and that, particularly recently, surgery may have a great deal to offer him under the proper conditions. Only with such patient awareness can one expect him to cooperate with his attending physician in obtaining maximum benefit from the various approaches to therapy. The patient must tactfully be informed how to live with his chronic disease and should know its name and appreciate its nature. It is often most tragically insufficient to inform the patient's relatives and leave him unaware. Under these circumstances the patient often suddenly and most disagreeably discovers the facts through inadvertence. He may be asked by a friend how long he has had his Parkinson's disease, or he may see an insurance application or a medical report. The fact that his trusted physician has withheld information from him logically leads him to conceive of Parkinson's disease in the same manner as people generally conceive of cancer, as an extraordinarily hopeless condition.

Our experience has shown that many of these patients entertain needless concern about brain tumor, impending insanity, and other irrelevant conditions. When we have had open discussions with patients who had been kept in the dark by other physicians, most have expressed resentment against their former medical advisers for the lack of honest information. In an investigation in 1957, we asked 300 of our patients whether

* This apparatus is manufactured by Fred J. Christensen, Harvard Medical School Machine Shop (Fig. 1).

they felt the physician ought to inform his patient about his Parkinson's disease as soon as the diagnosis has been established. Only one felt the physician should not do this.

Two recent examples follow.

1. A 28-year-old insurance executive developed a severe form of bilateral Parkinson's syndrome without tremor but with marked rigidity and akinesia. His internist referred him to a neurologist, who reported back to the internist and the patient's wife that the patient did have a severe form of the disease but admonished both to say nothing to the patient. The patient later saw a duplicate insurance form with the diagnosis and became most agitated. It has taken a good deal of effort to assuage his perturbation and blunt his resentment at the two former physicians.

2. One of us (R. S. S.), while on a recent trip to South America, saw the wife of a Professor of Medicine (at the request of her husband), who explained that she had had the condition for three years but had been told nothing. When this patient was questioned, she said, most surprisingly, "I have had Parkinson's disease for at least four years. I know my husband and his friends want to keep it a secret from me. How stupid do you think the wife of a professor is? I knew what it was because I had seen many people with it. I went along with my husband's plan and said nothing because he was clearly acting from the best of intentions." The professor was most amazed when this conversation was relayed to him and has the more keenly appreciated how much better it is to take the patient into one's confidence.

When the subject of discussion of the syndrome has been disposed of, the physician must then proceed to make every effort to have his patient in the best of general health. Because of the burdens of Parkinson's disease, other ailments are more distressing. There can be no disagreement about the need for regular annual physical examinations. When first seen, we have found it very useful to have the patient in the hospital for a week or 10 days for a complete medical evaluation and the beginning of general treatment. This would not apply to a very mild case in obvious good health, not requiring physical therapy, and with minimal early unilateral rigidity or tremor. Some of the patients so admitted to the hospital may have been on some anti-Parkinson medication before. In order to be economical and efficient one is often tempted to request the patient to drop his medication entirely for two days before admission to the hospital. This will enable the physician in charge to get a base-line study off medicine and see how severe the symptoms really are. One has to be very careful in doing this so that the Parkinson patient will not get into trouble from *acute withdrawal symptoms* as a result of precipitous elimination of his medication. It is most difficult to anticipate this, since some patients can drop their medicine and notice nothing uncomfortable or even any increase in symptoms for a number of days. Within 24 hours other patients will notice an unpleasant rapid increase in their symptoms, particularly tremor, a marked slowing in motor activity, and a disturbing sensation of fatigue, discomfort, and anxiety. In a number of instances, such symptoms have been quickly followed by nausea and vomiting with a marked increase in generalized tremor.

1. A 63-year-old woman with right-sided tremor and rigidity as a severe symptom over the past eight years and little involvement of the left side entered the hospital for neurologic evaluation prior to neurosurgical intervention on her dominant, or left, hemisphere. In order to see how severe the tremor was, the neurosurgeon had her drop her medication 24 hours prior to admission and continued withholding drugs for the first three days of her hospital stay. Very slowly over the first 36 hours the tremor became increasingly severer, and the patient was so handicapped that eating was impossible. At the same time she developed nausea, vomiting, and tachycardia to such a degree that the beginning of the neurosurgical work-up, which included pneumoencephalogram, had to be postponed for a week. Prompt restoration of medication (trihexyphenidyl [Artane] and diphenhydramine [Benadryl]) brought her tremor under partial control and eliminated the nausea and vomiting. In this case the total hospitalization during the neurosurgery was done while the patient was on her usual medicine.

2. A 51-year-old male attorney with a history of 11 years of bilateral involvement with both rigidity and tremor was admitted to the hospital for the purpose of evaluating the results of surgical intervention in his right, or nondominant, hemisphere a year previously and to decide about recommenda-

tions for a second operation on the dominant side because of the severe symptoms that had developed. He was requested to omit his medicine completely for 36 hours prior to admission (trihexyphenidyl and dextro amphetamine [Dexedrine]). During the first day of his hospital stay, while there was considerable increase in tremor on the side not operated on, the patient was still able to get around from the residual effects of his medicine. By the end of the second hospital day his drug-withdrawal symptoms, including tremor and the development of marked helplessness, akinesia, and "freezing," had reached such levels that he was completely helpless and immobile. His speech had become inaudible, and tremor and drooling had increased to such an amount that he was a pathetic sight. At this point his overconcerned and high-strung wife appeared. She was terrified and thought that a marked paroxysmal deterioration had occurred and that he would never be able to leave the hospital. She would not accept reassurance that these severe withdrawal reactions were always reversible and that it was otherwise impossible to know how ill her husband was in order to make the recommendation for the future. After 24 hours of the most unpleasant relationships, in which the medical staff was repeatedly accused of being cruel and unfeeling, gambling with human life, and wasting both money and time with unnecessary testing, the patient was restored to a better level of motor function by a newer regulation of oral medicine (Chlorphenoxamine hydrochloride [Phenoxene], Akineton,* and dextro amphetamine, schedules). Everything quieted down from this point, and the patient was discharged two days later. It was exceedingly important in this case to hold off medication until the severe degree of symptoms of akinesia and "freezing" under the category Y[4,8] had been ascertained, since these are strong contraindications for further surgery.

If symptoms of withdrawal intoxication appear, it is obvious that a base-line study is not feasible or practical and should be eliminated. During the first day of hospitalization we feel the following laboratory tests should be done:

1. White cell count and differential count and hemoglobin, blood cholesterol, and fasting blood sugar values, as well as two-hour postprandial blood sugar, N. P. N., and urine examinations. If it is possible to obtain a protein-bound iodine evaluation and a radioactive iodine uptake, these should be done, because a certain number of Parkinson patients will have high thyroid indices and may benefit from small doses of radioactive iodine. There is still a smaller number, in our own series not more than 5 out of 300, who actually have low-grade hyperthyroidism. When this is successfully treated, about one-half of these will show a considerable diminution of their tremor, feel better, and gain weight. In some cases this will allow them to drop their anti-Parkinson drugs for a period of time. However, we are absolutely certain that where the diagnosis of Parkinson's disease has been correctly made such a benefit is only temporary, lasting for some years, and is never associated with a so-called cure of the disease.

2. X-rays of the chest are important to obtain at this time. If the patient is in the geriatric group it is practical to get films of the upper legs and pelvis and lumbar vertebrae, looking for evidence of rarefaction such as osteoporosis, vertebral fracture, or dislocation that has not shown up clinically. In one patient we encountered a tuberculous cavity from the routine x-ray of his chest. He was a physician practicing in a South American city, and his chronic cough, weight loss, and excessive perspiration could have been explained by his advanced Parkinsonism. Thus the routine chest x-ray was very rewarding in this case. X-rays of the skull have contributed nothing in our opinion and might well be eliminated in such cases. Whenever possible an electroencephalogram should be done, since an abnormal one usually indicates symptoms in the Y- or Z-group. We feel that electrocardiograms are important to obtain at this stage of treatment because some of the patients show evidence of early coronary disease along with the Parkinsonism.

3. Careful routine neurological and medical evaluation should be done by the admitting physician, with special reference to circulation in the feet and presence or absence of edema in this area. Evidence of tenderness or discomfort in the abdominal cavity should be noted. Careful observation of the blood pressure and weight on entry should be made. As previously mentioned, many patients lose weight during the first three or four years of their disease, so this matter has to be investigated during this part of their study.

In our own hospital we like to have the patient seen by four consultants who constitute a team approach to the better management of these persons. In psychiatry, Dr. M. Chafetz is called on to see each hospitalized patient, and so is the chief of the physical therapy department, Dr. Arthur Watkins. Since we are both clinical neurologists, there is a consultation from a gastroenterologist, Dr. Perry Culver, and from our metabolic expert, Dr. Earle M. Chapman. Since many such work-ups will be done by competent internists, these latter

* 3-piperidino-1-phenyl-1-bicycloheptenylpropanol-1.

two consultants might be eliminated when the internist feels able to manage this problem alone.

Whenever ocular symptoms are encountered, such as visual difficulty suggesting glaucoma, an ophthalmological consultation should be obtained immediately and the entire work-up altered according to the advice of this consultant. Actually, we have not found that the oral doses of such drugs as stramonium or trihexyphenidyl are a hazard to the patient with glaucoma who has his increased ocular tension under control.

After some sort of base line is noted, drug therapy begins. Drugs may be started in small doses with rapid increments, since side-effects are easily handled in the hospital. Details of this will be covered later.

The physical therapist should begin his exercises on a daily program. He should, of course, realize that the patient is not going to be in the hospital for more than a week or so and will have to continue these exercises either alone, with his spouse at home, or with the help of a physical therapist who can see him two or three times a week. A program of self-exercise with instruction is particularly important to the spouse and should be obtained from the

MASSACHUSETTS GENERAL HOSPITAL UNIT#

NAME [redacted] DATE 6-7-57.

Name or abbreviation of medicine	After break.	After lunch	After supper	At bed.	Instructions
1. KEM. 5mg.	½	½		½	3 days
2. KEM.	½	½	½	½	5 days
3. KEM.	1	½	1	½	5 days
4. KEM.	1	1	1	1	Continue (Tc.)
5. ADD THEP. 25 mg.	1	1	1	1	Continue (Tc.)
6. IF TREMOR IS STILL PRESENT ADD:					
7. PAR. 10 mg.	1	1	1	1	1 week
8. PAR. 10 mg.	2	2	2	2	1 week
9. PAR. 10 mg.	3	3	3	3	1 week
10. PAR. 50 mg.	1	1	1	1	Continue (Tc.)
11. IF DROWSY FROM ABOVE ADD FOURTH DRUG:					
12. DEX. 5 mg.	1	1			Continue (Tc.)
13.					
14.					

This medicine stopped because side effects
Reduced amount per dose no benefit other
Reduced number of doses ran out

SIDE EFFECTS:
1. drowsy all the time
2. jittery or nervous
3. nausea
4. no appetite
5. headache
6. couldnot sleep
7. confused, dull
8. disturbed at night
9. symptoms worse
10. other
11. excessive dry mouth
12. severe blurred vision
13. bladder trouble
14. severe constipation
15. dizzy

Instructions: usually take the medicine until disagreeable side effects occur then go back to previous amount that had no such bad signs, but stop the medicine if severe symptoms occur.

Telephone report Drop post card Wait until next visit

Tc--take until further notice without change

T-d--take for_____number of days then increase as indicated on next line

---

Str. Stramonium
Hy. -Scopolamine
Art. -Artane
Pag. -Pagitane
Kem. -Kemadrin
Par. -Parsidol
Cog. -Cogentin
Pan. -Panparnit
Amb. -Ambodryl
Ben. -Benadryl
The. -Thephorin
Dex. -Dexedrine
Benz. -Benzedrine
Met. -Methedrine
Rit. -Ritalin
Metr. -Metrazol
Tho. Chlorpromazine
Equ. -Equanil
Mil. -Milltown
Ser. -Reserpine

Chart 2

physical therapist during this period of hospitalization.

When the patient is in the hospital for this type of therapeutic general work-up, he should not be kept in bed but should be encouraged to be as active as is allowed on the wards, moving about as frequently as he can, so the penalities of enforced bed stay will never occur. When he is ready for discharge, at the end of this period, the physician should plan a program that will cover the next six months and plan to see him for follow-up within two to three weeks of discharge. It has been found that the best times for the patient to take medicine at home is after meals and at bedtime. Since some of the schedules which have been worked out for the Parkinson patient are rather complicated, and sometimes very elaborate, we have used a form with a series of lines on which the medical schedules can be written, a list of the symptoms of overdosage, and instruction so that the patient will know what to do (Chart 2). The problems of constipation and nutrition, as well as some effort at neutralizing any reactive depression, should be part of the therapy planned before the patient leaves the hospital. In such a setting it is possible to start a number of different pharmocological preparations under hospital observation, where side-effects will not produce awkward situations in contact with the public.

We would estimate the period of a two-week stay in the hospital to be the equivalent of about four months' out-patient study. Sometimes patients are fearful of hospitalization. In such cases, if the initial management has to be taken care of in the office, it will be necessary to see the patients at frequent intervals, at first. The administration of drugs must be watched rather carefully until the patient's tolerance or sensitivity is known. We consider it essential in our own offices and clinic to obtain the weight and blood pressure of the patient on every visit. Many of these patients require some dietary supervision and instruction in order to get back to their normal weight. Nutritional need must be considered. The physician must explore carefully his patient's ability to handle food and fluid in order to make proper recommendations. Patients with awkwardness in eating will often abstain from trying to eat in public and must sometimes be urged to eat in private. Seventy-five per cent of Parkinsonian patients have a weight loss below optimal levels. We have often seen such undernourished patients repeatedly investigated for possible cancer when the real explanation was inadequate eating arrangements. One must remember that severe malnutrition can actually endanger the life of the Parkinsonian and enhance his muscle weakness and performance. A weight record is highly important. Simple suggestions to combat weight loss include supplementary meals, a polyvitamin preparation, particularly a readily absorbable one, and diets planned and specified in detail by a nutritionist. An electric hot tray is useful to keep meals warm for the very slow eating pattern that many develop. Electric food macerators help where chewing is troublesome from poorly fitting dentures or difficulties in using these due to tremor of the lips.

A 67-year-old retired physiology professor with Parkinson's disease lost weight steadily over five years, so that, in June 1958, she was 19 lb. under her initial weight of 122. For a month she was given vitamin and protein supplements and a carefully written diet of high caloric value. She continued to lose weight, and so on Oct. 10, 1958, she was down to 98 lb. At this point, a neighbor commenced to supervise her meal preparation and servings on a salary basis from a special fund of ours. We wished to test our opinion that weight loss was simply a matter of insufficient calorie intake and not an intrinsic part of the disease. A bonus was offered if the patient would gain weight. This promptly resulted in a weight gain of 7 lb., with correspondingly gratifying improvement in outlook on the patient's part. After some discussion, the neighbor ceased her effort, but the patient is now more aware of the importance of food intake and has continued thus far to gain weight. The physician must be prepared to offer such material solicitude to his patients at times.

Dependent edema of the ankles and feet is often a perplexing problem of a nonspecific nature. Here there is usually no element of cardiac failure; malnutrition and impaired blood osmotic pressure may play a minor role. The chief factor is disuse of the normal muscle-powered valved pumps for proper antigravity return of blood and lymph to the body. The swollen, uncomfortable legs offer an added reason for the Parkinsonian patient to be even more immobile. The use of a low-salt diet with mercurial and sulfonamide diuretics has its place, but the physician must place his primary reliance upon a regimen of regulated exercise and prescribed walking, sometimes with the aid of the modern nylon elastic stocking which is so inconspicuous.

Another general medical factor is a strong tendency to constipation, which offers an obvious threat to the patient's well-being. Particularly is this so because the common medications used in the condition are anticholinergic and enhance this state. Thus, our consultant, Dr. Perry Culver † contributes this summary.

Constipation is a frequent and troublesome complication of Parkinson's disease and occurs in 75% of all patients. Although some patients give a history of bowel difficulty prior to the onset of the symptoms of Parkinson's disease, many more develop constipation along with the classical symptoms of tremor and rigidity. Administration of various drugs for the relief of Parkinson's disease usually aggravates the difficulty in bowel evacuation.

The pathologic physiology of constipation in Parkinson's disease has not been elucidated. Patients often complain of inability to exert sufficient abdominal pressure to accomplish an evacuation. Many have a feeling of pressure and blockage in the lower sigmoid and rectum. Although the stools are usually hard, dry scybala, there is also difficulty in passing soft, semiformed feces. Sigmoidoscopic examinations have shown blushing, spasm, and an outpouring of mucus, all characteristic changes of a spastic colon. Attempts to improve bowel evacuation by the use of neostigmine bromide or other parasympathomimetic drugs have met with failure. Consequently, one can speculate that the brain lesion of Parkinson's disease may also involve the autonomic nervous system in such a way as to modify gastrointestinal tract function and result in an irritable colon syndrome.

Based on this postulation, a regimen similar to that employed in the management of spastic colons has been applied empirically to the treatment of constipation in Parkinson's disease with moderate success. In this program, there is emphasis on diet, anticholinesterase drugs, and patient education to overcome undue preoccupation with the bowels.

Without being unduly rigid, the diet should be free of roughage, spices, chocolate, and coffee. Iced foods and drinks may increase the irritability of the colon. At times, a lack of appetite and weight loss present real problems. Emphasis should be placed on a bland, high-caloric, high-protein diet.

Laxatives may be temporarily effective but soon cause more stubborn constipation because of increased bowel irritation. The use of nonirritating, hydrophilic, bulking agents, such as psyllium hydrophilic mucilloid (Metamucil), tend to keep the stools soft and aid in proper evacuation. Since spasticity of the colon seems to underlie the constipation, anticholinesterase drugs have been employed with benefit. Since solanaceous drugs, such as belladonna derivatives, and the newer synthetic parasympatholytic drugs must be used for the reduction of rigidity of muscles, undesirable side-effects of these increase the spasm of the lower colon. In our experience, dicyclomine (Bentyl) hydrochloride in doses of 10 to 40 mg. four times a day is an exception in that bowel spasm is relieved without untoward reactions.

Many patients with Parkinson's disease are unduly preoccupied with their bowels; at times this amounts almost to an obsession. An important part in the management of constipation is education of the patient. He must realize that daily bowel evacuations are not necessary and that conscious disregard of the intestines will lead to more normal function. It may take much convincing to persuade the patient to abandon enemas and laxatives. In most cases, acceptance of the program suggested above together with a regular time of going to the toilet, preferably after a meal, when the patient can relax, will result in a gradual return of normal bowel movements. One of the most important habits to develop in such a patient is to maintain a full daily ingestion of fluids, water, fruit juices, ginger ale, etc.

Urinary difficulties in men must be adequately investigated urologically. A mild median bar hypertrophy of the prostate under normal conditions might be no handicap, but in the Parkinson patient it may prematurely increase urinary retention with serious complications. Hypertension is

† Clinical Associate in Medicine, Harvard Medical School, and Chief, Gastro-Intestinal Clinic, Massachusetts General Hospital.

often encountered in the older group of patients; this causes no particular difficulty in itself and merits handling only for its own implications. It is not specifically part of the Parkinson syndrome.

VII. Psychiatric Management

Evaluation of mental function in our psychological testing laboratory has frequently shown some diminution in mental capacity at the time the patient with Parkinson's disease seeks medical help or thereafter. This may be somewhat difficult to estimate because of the physical slowness of the patient's means of expression (his voice and hands). Often there is no perceptible change with ordinary evaluation or precise psychological tests. Yet awareness of the existence of substantial mental deterioration is important to the patient's physician. It does not augur well for the success of either medical or surgical therapy.

In 1942, Benda and Cobb[11] noted that there had been only a small amount of speculation in the literature about psychic factors complicating or even causing the syndrome. There has been really no change in this view, and it is generally accepted today that onset following a particularly severe emotional stress is a coincidence reflecting merely exacerbation to a point of awareness of previous subclinical symptoms. On the other hand, everyone who has dealt with these pathetic patients is well aware of the impact of the loss of motor performance on the psychic well-being of the person. As has been stressed, tremor and rigidity, important as they certainly are, form only one facet of motor impairment. Those subtle defects in synkinetic action, so difficult quantitatively to define and record, appear seriously to inhibit the person in many important ways. Although occasional patients manage to hold a position in the working world for a surprisingly long time after symptoms come on, one usually finds this is not the case. Thus, there is financial dependence early. When difficulties with simple personal acts arise, a physical dependence on others becomes mandatory. To the depressing aspects of loss of earning power are added a stultifying inability in many ways to care for one's self. Managing the problems of depression, withdrawal, and apathy has taxed the resources of the best clinicians, neurologists, and psychiatrists. Since we have had a clinical psychiatrist, Dr. Morris E. Chafetz,‡ closely working with us on this problem since 1949, his specific views follow:

The development of any chronic illness will result in an emotional response of varying intensity in any person. When the psychiatrist refers to the complications of personality factors on an illness, he usually is alluding to responses above an empirical norm. This is especially true in Parkinson's disease, because it is little understood by either the profession or the laity. In situations of limited knowledge, the prevailing reactions will involve superstition, anxiety and even hostility. Therefore, it is essential to understand how significant emotional factors are in this disease in order to utilize this information in tailoring management.

Once the diagnosis of Parkinson's disease has been established, certain evidence and behavioral responses should be looked for which will suggest that the patient may be above the norm in emotional reactivity. In a previous communication[24] various emotional responses to the onset of Parkinsonism were discussed. At the same time it was emphasized that the individual who experienced the greatest difficulty emotionally adjusting to the disease was the one who would be categorized as having an obsessive-compulsive personality structure. The intensity of drives, the emphasis on energization, the necessity for rigid control over emotional and other behavioral responses, the desire for anonymity, the avoidance of dependent relationships, and the abhorrence of "being obligated" singularly mark these individuals.

Beyond the pale of emotional reactivity of the individual, evidence suggestive of more serious psychiatric problems may become apparent. Abrupt changes in the patient's way of life unrelated to the symptom picture are important clues. The patient who precipitously terminates his life-long working connections on learning the diagnosis, or suddenly withdraws from previously gratifying social activities probably has psychiatric complications. An over-concern by the patient with the attitudes and opinions of others since the advent

‡ Instructor in Psychiatry, Harvard Medical School, and Psychiatrist to Parkinson Clinic, Massachusetts General Hospital.

of the illness, unusual drug sensitivity, difficulty in following medication regimes, feelings of helplessness or hopelessness, panic, emotional lability, futility of outlook due to heightened premonitions of a bedridden future, and inappropriate emotional responses to reality situations usually indicate complications beyond what may be expected as a normal reaction to Parkinson's disease.

The psychiatrist or psychiatrically oriented practitioner will treat this aspect of Parkinson's disease first by establishing a warm and understanding relationship with the patient. Then he will evaluate how the patient has previously adapted to the stresses of life, such as the stabilization of relationships in family, work, and social activities, responses to illnesses and problems, etc. At the same time, he will evolve an understanding of what the patient's mental image is concerning his Parkinson's disease.

Upon clarification of the nature of these emotional undertones, the physician will decide the length, type and duration of the treatment. In other words, some patients may only require reassurance concerning misconceptions of the illness. Others may need supportive psychotherapy, which will mean regular one to two therapeutic visits per week, where the underlying psychodynamic factors of the patient are brought to bear in strengthening the mental defense system. This helps the patient attain a previously successful level of adaptation to life. Parenthetically, slapping a patient on the back and telling him to stop worrying is *not* supportive therapy! In other patients with the proper intellectual capacity and flexibility of personality structure, intensive exploratory psychotherapeutic techniques may be undertaken with the goal of developing new psychological reaction-patterns to life.

Certain areas will require special efforts by the therapist. Emotional upsets intensify the symptoms of Parkinson's disease and may convince the anxious patient that the condition is rapidly progressive. This leads to further incapacity, increased self-concern, a vicious cycle. During these episodes the patient should be seen more frequently until the earlier symptom plateau has been reestablished. The active need to deal with the family's attitudes and clarify misinterpretations which will arise due to the variability of performance by the patient is an important function of the therapist. It is the responsibility of the physician to help the patient avoid any situation which will augment feelings of uselessness and being unwanted. This will include assisting the individual to decide in what areas independence should be maintained, and where acceptance of aid is indicated.

Group psychotherapy has been successfully used with Parkinson patients.[*] This was employed as a supportive technique with limited goals. Groups were confined to 6 to 10 patients, met biweekly for 6 weeks, and required an active, directing leader. The response was sufficiently gratifying to patients and it was recommended for utilization by nonpsychiatric physicians. The experience with groups of Parkinson patients revealed the distorted fantasies, masked emotions, and misconceptions patients and their families had concerning this disease, and the effectiveness of the group method for clarification and support.

After psychotherapy has been terminated, it may be necessary for the patient to have occasional visits from time to time with the psychiatrist, when overwhelming problems develop. With the former healthy relationship as a background, stabilization can usually be readily achieved.

Some more desperate psychiatric situations may appear requiring electric shock, institutionalization, and even lobotomy, but it is my opinion that by early and careful scrutiny and management of emotional components, these last-resort measures can usually be avoided.

Another viewpoint, however, has been expressed by Dr. W. W. Sargant,§ of London, whom we quote:

> There are, however, some psychiatric complications which do not respond either to individual or group psychotherapy. Some Parkinson patients are particularly prone to obsessional thinking and we know how resistant such personalities are to psychotherapy.
>
> In European literature good results have been reported with the use of modified leucotomy techniques confined to the lower medial thalamic frontal quadrant which relieve tension and obsessional thinking without producing significant mental or personality deterioration. Likewise certain severe cases, especially in obsessive personalities, can be helped by carefully spaced electric shocks. Care should be taken not to increase tension while endeavoring to relieve further depression with electric shock. In milder tension states meprobamate (Equanil, Miltown) and mepazini (Pacatal) can be used.

Another value of the experiment in group psychotherapy to our clinic has been to transmit its lessons to our own medical management of the patients. As a regional center of interest in Parkinson's disease, we have been privileged to participate in clinical trials of new compounds as they appear. Whether the patient's experience is favorable with any one new drug or, as is perhaps more commonly the case, unfavorable,

§ Director of Psychiatric Service, St. Thomas's Hospital, London, England.

he gets a feeling of interest and understanding, of working together with the physician, that is obviously satisfying. Further, our routine efforts at graphic recording of progress (or lack of it in various ways), already noted, form a focus of hopeful interest for the patients. These considerations are most important to patient and physician.

The orthodox psychiatric approach to sick people, with allowances for the emotional organization of the person before he was taken ill, plus thought for the relationships of family, friends, and the community, must always take first rank in the care of the patient. From the socioeconomic viewpoint, the physician is frequently asked to sign certificates of medical disability for Social Security benefits. We urge that a very liberal attitude be taken toward this kind of disability. It is so difficult for the patient to present to strangers the real proportion of his motor difficulty. Reactive depressive mental attitudes are certainly somewhat justifiable reasons for some of the disability as well.

VIII. Physical Therapy

With the cooperation of the Department of Physical Medicine, we have sent most of our patients for some help from modern physical therapy. Here, too, quantitative evaluations thus far have been most frustratingly inadequate. Doshay[36] has stated that physical therapy has to be the fundamental on which all treatment of Parkinson's disease is based. To us this seems an undue emphasis. Erickson, Clark, Mulder, MacCarty, and Clements have presented (1956)[37] a comprehensive system of physical exercises; they stated wisely, "The prevention of progressive disability in many patients depends to a great extent on their ability and desire to be active."

It probably is not true that disuse atrophy of muscle commonly occurs to any severe degree here. Certainly, the abnormal presence of both tremor and rigidity would seem to work against that. From physical therapeutic principles, joint motion difficulty ought to be more important. The patient who does not move his limbs through much of their normal arc is bound to acquire corresponding limitation of joint movement. This does not, in our opinion, appear as a formidable problem. Even the obvious deformity of dorsal kyphosis is not permanent. A patient who walks with his upper dorsal and cervical spine at an angle of more than 60 degrees from the vertical can be put in an almost normal upright position by rather marked extensor force without any real pain; the original bent posture very quickly and frustratingly reappears, of course. We have tried to have kyphotic patients sleep with appropriately placed pillows, so that the dorsal spine would straighten during rest; in the usual case the patient reports this is uncomfortable and returns to the coiled position in sleep. Further, even the deformity of hyperextended proximal phalanges with hyperflexion at the middle phalangeal joint, so common an end-result in extreme rigidity cases, is not so permanent as was formerly thought. It was the astonishingly prompt disappearance of this posture after an anterior choroidal artery ligation operation that encouraged Dr. Irving Cooper in his pioneer work in this field.[38]

It is more reasonable to consider that posture and gait are greatly disturbed in Parkinson's disease. Physical therapy then is an important aid in helping normal voluntary control, in reinforcing muscle strength, in preventing fibrous contracture joint deformity, and in encouraging normal actions generally. Dr. Arthur L. Watkins || has summarized his recommendations as follows:

> Patients with Parkinson's disease are often bothered by fatigue; their efforts to ambulate, for example, are accompanied by excessive muscular action against rigidity. We have found that a daily period of rest in the horizontal position, supine, so that they can gradually stretch out into maximum extension of the neck and trunk and ex-

|| Assistant Clinical Professor of Medicine, Harvard Medical School, and Director of Physical Medicine Department, Massachusetts General Hospital.

tremities is often helpful. This may be done in a Physical Medicine Department and then be followed by other therapeutic measures to be described.

Passive Stretching: These patients are usually appreciative of passive movements of most of their joints. These may be started in the recumbent position on a plinth following the period of rest. The usual procedure is to stretch the trunk and neck muscles, if they do not attain the neutral position by rest; and then to passively stretch the major joints such as the shoulders and hips through a full range of motion, 3 to 10 repetitions for an exercise. Emphasis is also placed on stretching the thoracic cage through shoulder and arm movements and by asking the patient to deep breathe to increase respiratory exchange. We have also found that deep breathing in itself may serve to relax some of the rigidity of the musculature, at least temporarily.

When there are deformities of joints as a result of disuse, passive motions of the small muscles of the hands may be most helpful in obtaining an increase of motion, followed by active exercises.

Massage and Vibration: Skillfully applied massage of a general nature may help relax patients and may really contribute to the welfare of a patient who is still able to continue a busy day at his work. A general body massage from 5 to 15 minutes is often relaxing and tends to reduce the amount of rigidity and sometimes even the amount of tremor present. It is our feeling, however, where the time allowed for physical therapy is limited, that massage can generally be omitted in favor of a more active exercise program. We have used cyclic vibrating massage mattresses and pillows, but have not found them to be as effective as manual massage. In our experience, this is not generally acceptable for the patient as a substitute for physical therapeutic measures.

Posture and Gait Training: One aspect of treatment for almost all patients with Parkinson's disease in the early stages is to emphasize correct standing, posture, and gait training. It is felt that these patients have to concentrate on improving their posture and gait, and simply by so doing under instruction, may postpone the deforming features so characteristic of advanced Parkinson's disease. When giving gait training, emphasis is placed on the associated movements of the hand and upper extremities during walking, standing, and sitting.

We have also found in some cases that resisted walking, in which the therapist offers resistance during walking by pushing against the trunk, is usually helpful in helping maintain proper strength of the trunk and walking musculature and may, in a short period of time, accomplish more in maintaining strength than in simple free walking.

Progressive Resistance Exercises: In a few cases of early Parkinson's disease the weak quadriceps mechanism seems to be an important feature in their symptomatology. Actual testing of strength, using progressive resistance exercise technics, has shown this to be true, and some patients seem to benefit by doing a routine of weight lifting with the quadriceps, of lifting a boot with weights to maintain musculature of the quadriceps. Many patients, however, do not tolerate progressive resistance exercises of this type because of easy fatigue, and we do not advocate it as a routine in any of these patients. In those patients that seem to benefit by resistive exercises, this is first done by manual resistance, and then, if this is felt to be effective, exercise equipment may be provided for further quadriceps exercises in the home.

The Electric Rocking Chair [¶]: Schwab and Braverman have developed and made available at cost an electrically operated rocking chair which has attracted some considerable interest by physicians and patients. This device with a moving arm rest and a properly adjustable moving foot rest operates at variable speed and most successfully puts most of the joints of the cervical and lumbar spine and those of the extremities such as wrist, elbow, knee, and ankle through a considerable range of passive motion. It is especially useful to combat dependent pedal edema in severe cases [Fig. 3]. It is usually set up in the home and used 3 to 4 times a day for 15 to 20 minutes at a time. Patients appreciate attention by physiotherapists encouraging them to walk with slow, deliberately long steps, and to put their arms and legs forcefully through certain movements. The purely psychotherapeutic benefit of such treatment cannot be ignored.

Functional Aids: Many patients are seriously disabled and cannot perform the simplest activities of daily living. In this condition, the combined efforts of occupational therapists and physical therapists, under the direction of a physiatrist, have much to offer. Certain functional aids may be utilized, together with training in their use. General conditioning exercises may counteract the effects of disuse and achieve a general improvement in health and morale. The frequency of treatments is a medical decision depending on the individual and his tolerance for exercises.

Thoughtful attention, in a sort of physical way, toward the patient and his abilities and inabilities is very rewarding. Simple, easily adjustable clothing is to be recommended. It is obviously better for the patient's mo-

¶ This chair is made at cost by the Electric Rocking Chair Company, 80 Church St., Lowell, Mass.

Figure 3

rale if he wears a loose sport shirt than to have him laboriously put on a conventional white shirt which requires someone to button it for him. Elastic-sided or zippered shoes, elastic shoelaces, self-retaining socks, elastic-waistband trousers, and such simplicities must be given constant thought. Defecation, a society-honored process for solitary performance, often presents much difficulty for the unfortunate sufferer and one which he may not mention to his doctor. A simple rigging for the elevation of the toilet seat, held by uprights about 4 in. from the bowl, allows one to clean the anus with toilet paper while still seated firmly. The Parkinson's syndrome patient thus may obviate the formidable difficulties of teetering in an acutely lumbar flexed position. Other devices may suggest themselves in suitable cases. One of us (R. S. S.) has long made it his custom to explain the principles and value of such ideas and offers a standing reward to his patients for good suggestions. Consequently, many have been offered.

IX. Drug Therapy

1. *Solanaceous Alkaloids.*—From 1892, when Charcot advocated scopolamine, until 1948, about half a century later, atropine, scopolamine, and stramonium were the only effective compounds in Parkinson's disease. The special value of the wine extract of belladonna root of Bulgaria (Raeff)[4] was shown to have been exaggerated. Atropine medications should be used carefully, reaching full doses only after trying a quarter of the regular dose for the first day or so. This is particularly true in the elderly patient. The important limitations are the common ones of the solanaceous group, namely, blurring of vision, dry mouth, and various forms of central confusion and dizziness. We urge that they be kept on reserve and not forgotten, for at times scopolamine, 0.3 mg., will control tremor when no other drug will.

2. *Trihexyphenidyl Drugs.*—In 1947, the synthetic antispasmodic trihexyphenidyl (Artane, Pipanol) was introduced for the tremor and rigidity of Parkinson's disease. It at once met with widespread acceptance (Corbin [1949],[39] Phillips et al. [1950],[40] and Schwab and Tillman [1949][41]). There were soon introduced the chemical congeners cycrimine (Pagitane) (Zier and Doshay, 1957),[42] caramiphen (Panparnit) (Schwab and Leigh, 1949),[43] and procy-

clidine hydrochloride (Kemadrin) (Schwab and Chafetz, 1955).[44] These medications have an obscure central action on both tremor and rigidity and are very helpful. We urge that they be the first used in the medical treatment of the condition. More recently, we have been favorably impressed with a fifth congener, 3-piperinido-1-phenyl-1-bicycloheptenyl-propanol (Akineton), which has been well tried in Germany.

These drugs are anticholinergic, like atropine, and have the same side-effects and limitations. Some have found that these, as well as other drugs, in 6 to 18 months may lose their effect and may then require substitution by other drugs. Others have noted that after such intervals more drug is required. These medications, like the others used for Parkinson's disease, should be very gradually increased until mild toxic symptoms show that no more will be tolerated. Then a slight reduction should achieve a good effect. We ordinarily advise medicine after meals, when it will be diluted by food, and at bedtime, thus in effect providing medicine every six hours.

3. *Antihistamines.*—These are a varied group of medicines having the power to alleviate the effect of histamine spray on guinea pigs and to counter the effect of histamine on isolated uterine muscle strips. The chemical formulae vary. Diphenhydramine was introduced by Budnitz (1948),[45] Montuschi (1949),[46] and others. Phenindamine (2-methyl-9-phenyltetrahydro-1-pyridindene bitartrate). Thephorin is also effective. Gair and Ducey (1950)[47] have considered the nature of the chemical effectiveness of these drugs. These drugs are to some extent apparently centrally acting in Parkinson's disease, again affecting both tremor and rigidity, and are limited by central toxic confusion and by dry mouth. We feel that their present place is to supplement the effectiveness of the trihexyphenidyl group, and we use them together. A very convenient way is to prepare with a pharmacist an elixir with one of the trihexyphenidyl group and one of the antihistamine drugs together. For example, we use procyclidine hydrochloride, 2 mg., and phenindamine, 25 mg., in 4 cc. of a cherry-flavored elixir. The liquid preparation is well favored by the Parkinsonian, who often has trouble with pills and capsules. The liquid dosage is also easily adjusted.

Benztropine (Cogentin) methanesulfonate is a chemical combining a tropine (atropine effect) and diphenhydramine (antihistamine) in the same molecule. Doshay has reported (1956)[48] extensively on 502 patients using this compound. It has some usefulness, but it is limited by a side-effect of drowsiness. It may be taken once a day, at bedtime, and with other drugs it provides a better balanced schedule.

4. *Nonhalogenated Phenothiazines.*—Pharmacologists have presented to the physician in the past 10 years the interesting phenothiazines, which have been shown to have such powerful and diverse effects on the nervous system. In veterinary texts, such as "Animal Diseases," an interesting yearbook of the U. S. Department of Agriculture,[49] phenothiazines are given much discussion as antihelminthics for dogs, sheep, goats, and cattle. French work, especially Bovet and Longo's introduction of the protection of nicotine tremor by various drugs in 1951,[50] called attention to the powerful inhibition of tremor by certain substituted phenothiazines and not by others. Physicians are by now thoroughly familiar with the powerful central nervous "tranquilizing" effects of the phenothiazines, so useful in clinical medicine and psychiatry. The halogenated compounds, by and large, possess this potentiality (see below), though some of the nonhalogenated compounds do so to some extent. But, as will be discussed below, all of the halogenated compounds appear to worsen the symptoms of Parkinson's disease and must be scrupulously avoided. A partial list of effective phenothiazines is as follows:

Diethazine (Diparcol) 2-diethylaminoethyl derivative

Promethazine (Phenergan) 2-dimethylaminopropyl derivative

Ethopropazine (Parsidol) 2-diethylaminopropyl derivative

Promazine (Sparine) 3-dimethylaminopropyl derivative

Mepazine (Pacatal) *N*-methyl-3-piperdyl methyl derivative

In agreement with Doshay, Constable, and Agate (1956),[51] we feel that the phenothiazines are most useful to combat tremor. It seems to us, they are most effective as adjuvants to a schedule including a trihexyphenidyl derivative and an antihistamine and must be employed in full dosage only after a very slow build-up from the smallest dose so side-effects can be avoided. The full dosage may, upon occasion, be rather huge. Dry mouth, urinary retention, and confusion are familiar side-effects; serious agranulocytosis and rashes are occasionally encountered.

5. *Analeptic Therapy.*—Physicians have for a long time noted the drowsy tendency of Parkinsonian patients, together with the "akinetic" tendency (Schwab, England, and Peterson).[27] It seems clear that a drug stimulating the higher centers ought to be very useful. Amphetamine and its congeners indeed have some value and ought to be tried in appropriate cases. An analeptic elixir devised by one of us, containing apomorphine, strychnine, and dextro amphetamine, has long been used in our clinic with some benefit. We have tried (cautiously) the monoamine oxidase inhibitor iproniazid (Marsilid) with varied and often disappointing effect; it appears to us a very hazardous compound to employ in this chronic condition. Pentylenetetrazol (Metrazol) has some value, and so has methylphenidate (Ritalin), both of which we often use with definite advantage. Benactyzine hydrochloride (Suavitil) has not appeared to have been of as much usefulness. We await further advances in this rapidly expanding field, which ought to provide the clinician with more efficient therapeutic weapons.

6. *Induced Hypothyroidism.*—Schwab and Chapman,[52] noting a physiologic tendency for the basal metabolic rate to be slightly elevated (but still euthyroid) in this disease, have for some time (1954), in suitable cases, therapeutically produced hypometabolism with radioiodine. A selected small number of patients have managed to gain weight, to have less tremor and less perspiration, and to feel generally improved. Any untoward symptoms of hypothyroidism may be easily regulated by oral thyroid replacement therapy. Bartels and Rohart (1958)[53] stress that a very careful exclusion of mild hyperthyroidism ought to be made, including a B. M. R. done under thiopental (Pentothal) anesthesia. They note that the tremor of hyperthyroid states is usually very different from that seen in Parkinson's disease. Reduction of metabolic rate, then, in the euthyroid Parkinsonian patient appears to be a procedure of occasional value.

7. *Drug Tolerance and Drug Sensitivity.*

A tolerance to anti-Parkinson medication, with resulting loss of its effectiveness, has frequently been mentioned. While we feel it may occur at times, it seems likely in many instances that the sufferer becomes impatient with the relatively small degree of relief obtained with any one regimen. He then reports that the drugs have lost their effect; the physician arranges other medicines which seem temporarily of some usefulness, but these in turn receive finally the same comment by the patient. Many times we have seen the same improvement, more subjective than objective, return when the same drug is presented in another form. "Tolerance," thus, may be a misinterpretation of subjective dissatisfaction with any drug therapy (which is, at best, only 25% effective in raising the patient's performance). Actual advance in the basic disorder is another obvious explanation.

The physician is more often frustrated by the very real problem phenomenon of drug sensitivity. The usual story is that a patient in the fifth decade appears with Parkinson's disease; he is given perhaps small doses of an antispasmodic and a phenothiazine. The therapeutic result may actually be quite dramatic; the patient is

most grateful. The improvement seems to obtain still for some years; perhaps with the subsidence of the sense of initial relief it is a little less but not substantially so. Ten to fifteen years later, the patient appears to have rather suddenly become more incapacitated. He returns asking for more or better drugs. The physician sees that the drug dosage is small, so he anticipates that an increase in the old medicine or new ones in larger doses may be helpful. The actual effect proves to be the reverse. Confusion, dizziness, intestinal upset, and dry mouth become so severe that medication has to be reduced even from its former well-tolerated level. Thus, as Porteous and Ross have said (1956),[54] exactly when the patient in his older years needs more help, he cannot even get the modest improvement which the average patient is so grateful for. We see no good solution to this quandary, though we would much like to have one. Procyclidine hydrochloride and phenindamine, in small doses, seem to us often to be tolerated where other medications are not.

X. Parkinson Syndromes Produced by Halogenated Phenothiazines

Early work already referred to soon showed that the original chlorpromazine (Thorazine) produced a syndrome with rigidity, flattening of facies, diminished voice, and some tremor, usually of the non-Parkinson intention type. Its beneficial psychological effect still obtained; in some state hospitals at the present the chlorpromazine-treated patients are colloquially called "the shakers," as they are so distinctively recognized at once. A similar state is also produced by the completely unrelated drug, reserpine. Indeed, some men, such as Brooks (1956),[55] consider that the appearance of the extrapyramidal signs is a special indication for psychological benefit. We regard it as futile to argue that this condition is "not really Parkinson's disease," as Hall, Jackson, and Swain have maintained (1956).[56] Many of the features are, indeed, present. There may be marked impairment of alertness, sensory input, and awareness, usually not seen in idiopathic Parkinson's disease. Of course, the condition is transient, clearing slowly on the average in about a week after cessation of drug therapy. Rashkis and Smarr (1957),[57] among others, recommend the use of the trihexyphenidyl group to counter the Parkinson syndrome symptoms while the chlorphenothiazine is continued. One of the drug manufacturers has actually informed us that his largest purchasers of the trihexyphenidyls are the state mental hospitals.

An even more dramatic picture is regularly produced in a small fraction of the patients treated with the fluorinated phenothiazines. In our area the most common offender is prochlorperazine (Compazine), as first noted by Delay, Deniker, Green, and Mordret (1957),[58] in France. Acute transitory psychomotor excitement, tremor, myoclonia opisthotonos (several patients were recently admitted to the Massachusetts General Hospital with the admitting diagnosis of tetanus), dystonic spasms, especially of the face and jaw, and oculogyric crises are prominent. O'Hara (1958)[59] noted five cases, two of which dislocated their jaws in spasms; Christian and Paulson (1958)[60] reported a most bizarre sequence of motor abnormalities.

A partial list of available halogenated Parkinson-producing phenothiazines is as follows:

Chlorpromazine (Thorazine) 3-dimethylaminopropyl derivative

Perphenazine (Trilafon) 3-(1-[2-hydroxyethyl], 4-piperazinyl) propyl derivative

Thiopropazate (Dartal) 3-(1-[2-acetoxyethyl], 4-piperazinyl) propyl derivative

Prochlorperazine (Compazine) 3-(1-methyl-4-piperazinyl) propyl derivative

The observations, then, that most of the features of Parkinson's disease have now in different ways been reproduced by these drugs seem to us highly intriguing on a speculative basis. In the past, carbon monoxide, mercury, and manganese intoxication have been implicated in tremor production. Here is a new set of compounds with even

more pertinent effects in the extrapyramidal area of the nervous system.

Since the number of available anti-Parkinson preparations that have been described in previous paragraphs may leave the practicing physician a bit confused as to the most efficient method of starting medical treatment of his Parkinson patient, we are summarizing some suggestions here that might be valuable.

If the presenting symptoms are chiefly rigidity with little tremor, the first drugs to be used are those of the atropine group, including trihexyphenidyl, cycrimine (Pagitane), procyclidine hydrochloride, and Akineton. Each one of these should be started with the smallest possible dose for a couple of days, to see the kind of sensitivity which the patient exhibits. Such a dose is usually one to two mg. of the above-mentioned drugs. If, after a few days, there is no sensitivity the dose should be slowly increased. If dry mouth or blurred vision occur, this indicates the approach of overdosage and the amount should be dropped back to a level that is comfortable without side-effects. If this is done, serious side-effects such as confusion and delirium are usually avoided.

If the Parkinson patient presents symptoms of tremor with little rigidity, it is better to start the treatment with one of the phenothiazines such as promethazine, ethopropazine, or mepazine (Pacatal). Here even more care should be followed in starting with the smallest dose possible. Commence with between 10 and 12 mg. two to four times daily and then slowly increase the dosage until side-effects appear. These may be drowsiness and dullness, as well as dry mouth; if so, the drug should be reduced to a more pleasant and tolerable level.

In such cases, where rigidity and tremor are strongly present, it is sometimes necessary to start out with very small doses of one or the other of the drugs mentioned and then add the second group later. After some kind of stabilization is reached, the patient can have other drugs added, such as the antihistamines previously mentioned, either diphenhydramine, phenindamine or triprolidine (Actidil). If the dullness and drowsiness appear to be present even with small amounts of these substances one must add an analeptic such as dextro amphetamine, methamphetamine, or methylphenidate.

It must be kept in mind that the patients in the X-group tolerate the drugs rather well. Those in the Y-group may show extreme sensitivity to certain ones but tolerate others, and the patients in the Z-group are usually intolerant of anything but very small doses. The older the patient is and the more feeble he is, the more careful the initial drug therapy should be. Overtreatment with these many different compounds occurs so frequently that special warning should be reemphasized at this point. A further warning seems appropriate here that the substances that produce Parkinsonism have no place in the treatment of patients with this disorder. These are prochlorperazine, chlorpromazine, and the rauwolfia alkaloids.

XI. Value of Special Hospital Care

In general, in the United States, patients who have severe forms of Parkinson's disease or who are severely disabled by their symptoms, and cannot be looked after at home, are sent to nursing homes if they can afford them or occasionally are forced to be committed to state hospitals for the insane or at best enrolled in chronic hospitals for the disabled and aged. Owing to the special limitations and symptoms associated with Parkinson's disease and the requirements for specific individual therapy, such patients fare very poorly as a rule. Many people concerned with this disease and its management have wondered if special hospitals devoted to it could do a better job.

In Germany, in the city of Kassel, there has been such a small hospital in operation since 1932, called the Koenigin Elena Klinik. This hospital consists of a remodeled country estate and has room for 125

patients. Some of the patients are in small rooms with three or four beds. In the various outbuildings of the estate physical therapy units, occupational equipment, and so forth have been set up. Numerous outdoor aids to the rehabilitation of walking and so forth have been erected. When visited by one of the authors (R. S. S.) in July, 1957, this hospital was in charge of Dr. H. P. Schulz. He had two medical assistants and an adequate number of nurses and physical therapists, etc. The plan of treatment was to keep each patient busily and actively occupied from seven in the morning until six at night. Individual and group physical therapy were the main part of the program; speech therapy and group lessons in singing and so forth were practiced, and, particularly during the summer months when patients were outdoors, there was a vigorous program of gait training, with mechanical supports and individual assistance. Patients were kept there from two to three months at a time and then returned to their homes. Various types of pharmacological therapy were used in conjunction with the previously mentioned treatment. It is claimed by the director that three-quarters of the patients enrolled there were improved significantly at the end of their stay and that half of these retained the level of their improvement at home. A small number would come back from time to time for a sort of postgraduate course for a few weeks. On the other hand, various neurologists in Germany stated that they believed the patients benefited in the special clinic but reverted back to their previous levels at once on returning home.

One of our patients was sent to this special hospital in the summer of 1958 for a period of two months. Since we had adequate information about her prehospital condition, we looked forward to assessing her level of improvement on return to the United States. We were very much disappointed to find that nearly all of her signs and symptoms were about the same as on going there. Her motor performance in the various fields that we had tested had only changed favorably in one respect, namely, in her walking. The most that we could measure was a 10% increment in general motor ability, and this is actually within the spontaneous variations of most patients over periods of several months.

In our own local area the state has provided a very modern, new, and adequately equipped hospital for the rehabilitation of patients with chronic diseases, called the Lemuel P. Shattuck State Hospital. Since 1956, under the supervision of Dr. William Timberlake, patients with Parkinson's disease have been admitted to this hospital for rehabilitation. They remain for two to three months and receive the most modern drug treatment available and very comfortable and pleasant accommodations. Physical therapy of a very modern and efficient type is available, but there is unfortunately a shortage of trained personnel to administer it. No hour-to-hour schedule similar to the German clinic is possible in this institution. Results of such hospitalization have been rather disappointing. Most of the patients do not show objectively significant changes in their motor performance in spite of as much therapy as we can give them. About one-quarter, however, leave the hospital in a better nutritional state, with elevation in their mood, and some 5% to 10% improved in their motor performance.

Under the direction of Dr. Sedgwick Mead, a special rehabilitation hospital exists in Vallejo, Calif. He reported in 1958[61] that he has made a special effort here to take care of the difficulties of his Parkinson's patients in the hospital and feels that progress has been made in teaching them to get along more efficiently, in spite of their physical handicaps. Statistics as to how successful they are are not yet available, but certainly it is worth while developing places of this sort.

XII. Surgical Intervention

The history of this aspect of Parkinson's disease is well presented in Irving Cooper's recent monograph.[38] The surgical procedures that have been tried, such as inter-

ference with the ventral pyramidal pathway in the cervical spinal cord (Putnam [1950],[62] Ebin [1949],[63] Oliver [1953][64]), with the anterior limb of the internal capsule (Browder[65]), and with premotor cortical resection (Klemme, 1940),[66] usually left the patient with a spastic weakness.

For many years it was believed that tremor and rigidity could be relieved only in direct relation to the spastic weakness produced by damage to the pyramidal pathways. In addition, the cortical extirpative procedures often entailed postsurgical epilepsy. Although any large clinic usually has patients successfully treated without spastic weakness, these are the exceptions which prove this rule (Alajouanine, 1957).[67] We are reminded of the surprises from these procedures by the practically perfect relief of unilateral tremor obtained by cortical resection in 1941 in a railroad fireman who still occasionally attends our clinic. He is entirely satisfied; objective neurological signs of tremor are not present, and signs of spasticity are absent. He does have focal epilepsy, but diphenylhydantoin (Dilantin) affords complete control. At the present time, operative intervention on the cervical cord, internal capsule, subcortex, and cortex are no longer recommended. A. Earl Walker[68] does have some reservations concerning procedures on the cerebral peduncles, where function and operative intervention are incompletely understood.

Russell Meyers,[70] as long ago as 1941, presented a small number of patients with Parkinson's disease who were benefited markedly by selective lesions produced in the ansa lenticularis. His operations were very formidable, however. Spiegel and Wycis (1954)[69] began to devise a stereotactic approach to the region of the globus pallidus and its outflow at this time. It was Irving Cooper's accidentally good result in tying one anterior choroidal artery, inadvertently cut in a patient with tremor and rigidity operated on for the purpose of cutting the extrapyramidal fibers in the cerebral peduncle, that drew his attention to the watershed of this small artery. It includes part of the choroid plexus but also parts of the hippocampus, insula, hypothalamus, thalamus, globus pallidus, and putamen. Although anterior choroidal artery ligation proved a procedure with a somewhat high mortality (10% to 15%), when generally done in patients with severe degrees of tremor and rigidity, there seemed no doubt that improvement was often extremely dramatic and associated with little or no spastic weakness. Cooper then turned his attention to other procedures affecting the internal third of the pyramidal-shaped globus pallidus (and later the ventrolateral nucleus of the thalamus). He, together with Pouloukine and Bravo,[71-73] developed a double-lumen catheter with a small inflatable balloon, inserted through the posterosuperior aspect of the frontal lobe with a stylet in a stereotaxic guide with pneumoencephalographic and radiographic control. After the proper location of this catheter, the balloon is inflated for a day or so, then deflated and the cavity filled with a small amount of viscous absolute alcohol in methylcellulose (Etopalin, Ciba). The catheter is left temporarily in situ, and later very tiny increments of the liquid may be added. Their series is now approaching the extraordinary number of 1,000 patients operated on. Their mortality in the first 700 is reported at 2% and serious operative morbidity at 2%. Cooper's initial development of these techniques has been followed by neurosurgeons at other medical centers. There is no question that this work represents an important advance in the understanding of Parkinson's syndrome.

An entire number of the *Journal of the American Geriatrics Society* is devoted to a critical discussion of his work. Schwab and England (1956)[32] had the privilege of examining 26 of his selected cases and reported confirmation of most of Cooper's claims with those patients.

Other surgeons are exploring different techniques for making lesions. Narabayashi and Okuma (1956)[74] have used procaine in oil injected into the globus pallidus. Riechert,[75] Guiot and Brion,[76,77] and Fen-

elon [78] present smaller series with electrocoagulative methods. Russell Meyers [79] makes destructive lesions in the substantia nigra by focused ultrasound rays. Walker [68] has discussed a small number of cases with injection of radioactive yttrium, while Talaraich [80] employed radioactive gold. In our hospital, W. H. Sweet has tried radiofrequency coagulation combined with alcohol injection. Walker considers [68] that "hemiballismus, Parkinsonian tremor, choreoathetosis, and dystonia may thereby respond in this order of diminishing effectiveness." Other neurosurgeons will have different opinions about details. As we view the matter, improvement in certain favorable cases from surgical intervention on the globus pallidus, its outflow, and the ventrolateral thalamic nucleus on contralateral tremor and rigidity is most dramatically superior to the usual result with medical treatment. Complete control of these symptoms may not infrequently be encountered; pyramidal spasticity and weakness is fortunately, in the majority of cases, only a temporary complication. About 12% seem to have residual pyramidal tract signs, such as a unilateral Hoffman sign or very lively tendon reflexes.

It appears to us that the benefit, by and large, is under the Group X of our clinical description of Parkinson's disease (contralateral tremor and rigidity). When one turns to the more complex functions of the Y-group related to posture, gait, etc., the possible improvement with surgery in the internal pallidal or thalamic area appears somewhat more limited. The improved motor ability of the side successfully operated on will entail a definite amount of improved ease of walking and standing. The frequent return of associated arm swing in gait seems particularly impressive (drugs may occasionally affect this result, too). However, generally, the akinetic tendencies remain, pulsions are seldom completely eradicated, kyphotic postures tend to persist, and micrographia is not abolished. Disorders of complex coordination and synchronization, thus, do not respond as satisfactorily as do tremor and rigidity. When we turn our attention to the Z-group we find even less predictable improvement. Sialorrhea, dysphonia, and dysphagia are seldom relieved; loss of facial expression, blepharospasm and marked glabellar reflexes are not ordinarily changed. (There are, it is true, fortunate exceptions to this general conclusion.) It may, therefore, be considered that disorders in Parkinson's disease associated with Groups Y and Z may not be expected to improve significantly.

This has allowed us to clarify our thinking about the indications for surgical intervention in Parkinson's disease. The ratio of the degree of incapacity caused by tremor and rigidity on any one side compared with the degree of incapacity caused by complex bilateral disorders of gait, stance, and action, and particularly with that caused by cranial nerve disorders, is critical when considering surgical intervention. To some degree, physiologic age per se is also a contraindication; it is generally an empirically derived impression that patients over 65 do less well. Severe bilateral tremor and rigidity are often associated with the complex Y-category of abnormality; this augurs less favorably, especially since it is surgical experience that unknown factors affect a second operation on the other side. It is more hazardous, lesions must be smaller, peculiar states of lobotomy-like indifference may come on (Hassler and Riechert).[81] Tillmann and Schwab [82] have emphasized that there is a type of favorable patient who strongly seeks relief and psychologically desires very much to improve. A recognized ardent desire and enthusiasm on the part of the patient must be given affirmative weight, providing this is not based on false concepts of what surgery may offer.

It is only natural that less severely afflicted patients, particularly those with predominantly unilateral manifestations, will be themselves inclined to defer surgery. When the tremor and rigidity are in the nondominant hand, little disability results, but if it is in the dominant one, much more

trouble exists. Here surgery may appear necessary earlier. Certainly, it is an elective procedure; it may often be put off a long time. Serious incapacity, usually with loss of earning power, is the deciding factor in the minds of most clinicians with experience in surgical and medical therapy. For instance, M. R. Houdart,[67] a neurosurgeon discussing the point in a symposium with T. Alajouanine and others, says he will not operate on anyone who can still earn any substantial part of his living; others have said the same. It is obvious that close collaboration of internist and surgeon here is most rewarding. Drug requirement may be surprisingly diminished or even eliminated in the patient successfully operated on. It may still be necessary in judicious quantities; special care is often still required.

The natural explanation of these destructive surgical lesions at the present time lies in theoretical speculation. A glance at Fulton's neurophysiological text (1943)[83] will indicate how the procedure conflicts with what was previously considered the physiology of the globus pallidus and its suppressive regulatory nature of extrapyramidal movement. To explain the new observations, Stanley-Jones,[84] for instance, offers an *ad hoc* argument that the improvement depends on the differential degree of interference of pallidal lesions on the small (95%) and large (5%) cells in the globus pallidus and with their connections inferiorly. He speculates that, depending on the restoration of a state of equilibrium of various suppressor networks emanating inferiorly, spasticity, paralysis agitans, and rigidity may be improved. Guiot[76] recently admits his own difficulty in comprehension of mechanisms, while Walker[68] offers a number of suggestive deductions. Certainly, our experience with electrodes left in situ discloses no characteristic electrical discharges in the area. Haynes, Meyers, and Knott (1949)[85] and Spiegel[86] report the same.

Without elaborating further on neurosurgical procedures, we would like to insert a comment about the euphoria which appears with some patients operated on. Close observation of these patients has convinced us that this is in our cases not a pathological result, not a state of bland indifference produced by interference with emotional pathways in this vital region. It rather seems, in some part at least, to be a psychological relief, a sense of happiness and exhilaration in the ability to move and express one's self in a greatly facilitated manner. It seems often to be a lasting sort of thing (really the soul-satisfying reward that any surgeon hopes for and may often not get).

The reported favorable results of this type of basal ganglia surgery indicates that some 70% to 80% are objectively benefited for as long as they have been followed (which is now one to six years). It seems that many will continue to hold their benefit longer. Some progress on the other side and lose their gains in this way. It would appear true that even in this group, their state, had they not been through their operation, would have been much more incapacitating. There is a mortality rate of approximately 2% and a complication rate of an additional 2%. In our experience with surgical intervention in 85 of our patients the benefit was somewhat lower, namely 65% in 55 (Cooper) and 37% in 30 (Sweet).

It appears that for every 100 patients with Parkinson's disease there are only 1 or possibly 2 that are ideal for this kind of surgery, and perhaps another 10 or 12 who will derive some benefit of a worthwhile type but will still have to take medication and other forms of therapy. In the 1% or 2% that are ideal the degree of relief is spectacular and most impressive, and we have not reached such levels of disappearance of rigidity and tremor by the use of any drugs mentioned in this paper.

XIII. Summary of Problems in Management

The difficulties have already been mentioned above to some extent. The disease appears to have diverse causes, each with a different and unpredictable course, asso-

ciated with variations from hour to hour, day to day, and year to year. Emotional factors, especially the degree of anxiety and the intensity of motivation, affect motor performance strikingly. Associated mental disorders and medical disorders are often encountered to complicate therapy. Our present clinical criteria for evaluating patients have only rough reproducibility.

It must then be admitted that the treatment is largely medical, both a general supportive sort and more or less specifically with drugs, which have only a small and somewhat irregular effect. Drug tolerance and drug sensitivity present important drawbacks. Most effective drug schedules, even when side-effects such as drowsiness are partially overcome by stimulants such as amphetamine, are only compromises. Some penalties must be paid for drug-reduced tremor. This may not bother a simple elderly patient, but it may upset his relatives and friends. To this unsatisfactory state now appears surgical intervention with destructive lesions, without sound understanding of the physiological background. At the present time we say that any real treatment must be the result of constant cooperative work between the medical man, the surgeon, and the laboratory, with important assists from the psychiatrist and physical therapist.

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Reviews of Internal Medicine

Corticotropin (ACTH) and Adrenal Steroids in Liver Disease

A Critical Review

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Introduction

Corticotropin (ACTH) and adrenal steroids in recent years have gained a prominent place in the therapeutic armamentarium of human disease. While their biologic and pharmacological actions have been studied extensively, these compounds often are prescribed, without apparently sound scientific basis, because of the absence of more effective measures, in severe life-threatening diseases. In the course of other studies, it appeared useful to review the readily available medical literature and to evaluate the usefulness and the limitations of these drugs in hepatic disease.

Corticotropin and adrenal steroids have variable physiological and pharmacological effects in different species of animals. According to Long,[1] mice, rats, and rabbits are cortisone-sensitive, while guinea pigs, monkeys, and men are cortisone-resistant. The effects of these substances also vary according to the dosage. A "moderate" therapeutic dose of adrenal steroids may exercise beneficial physiological effects, while large doses may be harmful. Basically, steroids are anabolic,[2] and adrenalectomized animals grow faster and their nitrogen balance becomes more positive than untreated controls; only in excessive quantities will these agents suppress anabolism.[2]

Adrenal steroids have been found to inhibit all phases of the inflammatory response to mechanical or chemical injury.[3] They may suppress fibroblastic proliferation and budding of new capillaries, and they may prevent granuloma formation.[4] They reduce capillary permeability,[5] and this effect may be important in the mechanism of action of these hormones.[6] Adrenal corticoids seem to exercise an important influence upon immunological phenomena. According to Germuth and Ottinger,[7] corticotropin and steroids decrease the ability to produce antibodies in sensitized rabbits; the skin of the animal retains the capacity to react when antibodies are injected locally. Dougherty and Schneebeli [8] demonstrated, in cortisone-treated mice, that the allergic inflammation was greatly diminished and shortened. These compounds minimize the inflammatory vascular reaction in serum sickness and in the experimental tubercular infection, as studied by the ear chamber technique.[9,10] The blood of cortisone-treated animals [11] had a slightly reduced bactericidal effect when compared with that of untreated animals, and there was a slight reduction of the opsonic index. Other reports are less unequivocal in their conclusions. Havens et al.[12] did not find any difference in diphtheria antitoxin production in patients treated and nontreated with steroids. Lovell et al.,[13] on the basis of well-controlled experiments, concluded that steroids had little or no effect on mechanisms of histamine release but seem to act on the delayed type of hypersensitivity of the human skin.

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What is the action of corticotropin and steroids upon the liver? Long et al.[14] have demonstrated a remarkable increase in liver glycogen in adrenalectomized mice when treated with corticoids. Germuth et al.[15] found a trifold increase in liver glycogen in sensitized rabbits treated with cortisone, as compared with untreated animals. Glycogen is known to have a protein-sparing effect on the general metabolism; it enhances production of plasma proteins and increases the deposition of new protein in the liver.[16] Cortisone also has a direct influence upon the protein content of the liver and the blood plasma. Well-controlled and confirmed experiments of Clark[17] indicate that cortisone-treated animals have large livers with a higher protein content than untreated controls; the plasma albumin in treated animals also is increased.

Corticotropin and steroids seem to play a role in fat metabolism.[18] Cortisone was found[19] to increase the total fatty acids and blood cholesterol levels in rabbits. There also was a significant deposition of fat in the liver. On the other hand, detailed histopathological studies did not reveal fatty infiltration in the livers of rats on short-term treatment with cortisone.[20] Pretreatment with cortisone prevented carbon tetrachloride injury in rats.[21]

Cortisone has a delaying action on hepatic necrosis in rats given synthetic diets.[22] In rats receiving carbon tetrachloride, cortisone reduced the amount of collagen and reticulum.[23] There also were fewer mitoses, less vacuolation of parenchymal cells, and considerable reduction of round-cell infiltration in the periportal areas. Cortisone[24] also delayed the mesenchymal response to foreign bodies implanted into the liver of rats. Regniers et al.[25] demonstrated the variability of the cortisone effect upon the cirrhosis produced by carbon tetrachloride. Cortisone given before the cirrhosis-producing substance precipitated the phenomena leading to cirrhosis; given simultaneously, it had a delaying effect, and when given after carbon tetrachloride, it reversed some features of the cirrhotic process.

Corticotropin and Steroids and Excretory Functions of the Liver

Solem and Olsen[26] observed a remarkable prompt decline in the icterus index in patients with infectious hepatitis given corticotropin. There was no such decrease in patients with extrahepatic obstruction treated similarly. Patterson et al.[27] performed duodenal drainage in normal persons and in patients with various diseases of the gastrointestinal tract. The duodenal content was collected at 15-minute intervals for 5 to 7 hours. After intravenous administration of cortisone, the concentration of bilirubin in the duodenal drainage increased substantially for a prolonged period. This phenomenon also occurred in cholecystectomized patients, suggesting that cortisone has a choleretic effect. Chalmers et al.,[28] in careful studies of total serum bilirubin in patients with extrahepatic obstruction receiving corticotropin, found a choleretic effect in those patients who exhibited a concurrent rise in fecal urobilinogen. There were, nevertheless, instances with a decline in serum bilirubin not accompanied by a rise in fecal urobilinogen. Chalmers et al.,[29] in a study of 41 patients with different liver diseases and jaundice, concluded that a moderate overlapping is observed when the effect of corticotropin is studied on the hyperbilirubinemia of hepatic or extrahepatic origin. If a reduction of 33% in total bilirubin after corticotropin administration should be considered a positive test, half of the obstructive cases were positive. They rejected, therefore, Solem's[30] suggestion to use corticotropin as a diagnostic test in the differentiation of intrahepatic and extrahepatic jaundice.

Shay and Sun[31] collected the bile through a T-tube inserted into the common bile duct in 10 postcholecystectomy patients. A single intravenous injection of 100 mg. of hydrocortisone did not increase the volume, the concentration of bile, and the total

bilirubin in the drainage fluid collected for four hours; no choleretic or hydrocholeretic action could be observed under the conditions of the study. Katz et al.[32] administered cortisone repeatedly to patients with intrahepatic and extrahepatic obstructive jaundice; lowering of the total and the direct-reacting bilirubin was observed in both type of jaundice; the decline was more pronounced in parenchymatous jaundice; in some cases, there was a lowering of urinary bilirubin. The authors suggested that cortisone may play a role in bilirubinogenesis. Clifton et al.[33] concluded that cortisone orally does not accelerate plasma clearance of sulfobromophthalein (Bromsulphalein) or the percentage disappearance rate of I^{131} Rose Bengal. Hydrocortisone intravenously did not alter the volume, the concentration of bile, or the total bilirubin output within a period of three hours. Ingelfinger[34] thus discarded the idea that the glucocorticoids acts as choleretics. Mainguet and Caroli[35] studied the fecal urobilinogen in patients with hepatitis and observed a drop in bilirubin levels under steroid treatment, with a pronounced rise in fecal urobilinogen; this then decreased further before rising to normal levels. The secondary fall of fecal urobilinogen was attributed to emptying of the canals of Hering by steroids, followed by their slow refilling. Recently, Summerskill and Jones[36] studied 12 patients with obstructive jaundice of uncertain origin and found a five-day trial of steroid treatment valuable in differentiating intrahepatic from extrahepatic obstruction.

This brief summary might suggest beneficial effects from corticotropin steroids in various types of liver disease. These would comprise illnesses involving nutritional factors, inflammation, and perhaps immunological phenomena.

The possible therapeutic effects of corticotropin and steroids in various liver diseases represents the principal interest of the present review. The first clinical attempts to treat advanced liver disease yielded variable results. Bongiovanni and Eisenmenger[37] found patients with advanced liver disease responsive to corticotropin. There was an increase in the urinary excretion of 17-ketosteroids and a decline in the number of circulating eosinophils. Liver-function tests did not seem to be influenced greatly. Brown[38] observed a beneficial influence on the accompanying anemia and, in serial liver biopsies, demonstrated a decrease in the amount of fat. Gyorgy[39] also observed less fat in liver biopsy specimens and a higher content in glycogen, in agreement with earlier experimental findings.

Corticotropin and Steroids in Infectious Hepatitis

This disease usually is a benign and a self-limited disease, but in a small number of cases it may become very severe, with progression to hepatic failure and death. It is difficult to predict the cases proceeding to this course; hence, the desire to utilize corticotropin and steroids in patients not responding rapidly. Thorn et al.[40] described a patient with aplastic anemia, complicated by hepatitis, responding to corticotropin; there was a dramatic increase in appetite, improved sense of well-being, lowering of body temperature, decrease in serum bilirubin, and improvement of liver-function tests. Colbert et al.[41] reported five patients with severe infectious hepatitis treated with intramuscular injections of corticotropin for periods up to eight days. Two patients experienced recurrences after the drug was discontinued. In all instances the serum bilirubin decreased; other tests were less influenced. Corticotropin was thought to be beneficial in this small series. McCollum,[42] while studying the size of the homologous serum jaundice virus, had three volunteers who developed severe hepatitis. Cortisone was administered at a dose of 100 mg. for 5 days and then at decreasing doses for another 20 days. There was an immediate beneficial effect in all three patients; one experienced a relapse when the dose of cortisone was decreased but improved promptly when a higher dose was resumed. The outstanding features were the decline in serum bilirubin and the sub-

sidence of clinical symptoms. Svartz [43] observed good results from cortisone in severe infectious hepatitis, with a rapid decline of fever and jaundice; she considered the role of cortisone to be life-saving. Suzman [44] described six cases treated with corticotropin intravenously. Two patients died—one after three days of treatment; the second regained consciousness but died on the 27th day of treatment from a massive gastrointestinal hemorrhage. Three patients were clearly benefited. In one patient, the drug was discontinued because of perforation of a peptic ulcer. Evans et al.[45] observed a dramatic decline of the serum bilirubin and symptomatic improvement in patients treated with corticotropin. However, the duration of the disease did not appear shortened when compared with that of the controls. Analysis of patients who received corticotropin within the first 10 days after appearance of symptoms revealed more side-effects and prolongation of the disease period than in those who received corticotropin in the second 10 days of illness. No difference was noticed in serial biopsy specimens between the corticotropin-treated patients and controls, except for more fatty infiltration in three patients of the corticotropin group. The decreasing effect of corticotropin with progress of treatment suggested that the adrenals may respond progressively less well in patients with acute hepatitis. In a further study,[46] 10 patients were treated with cortisone within 10 days from the onset of symptoms. Both the serum bilirubin and the sulfobromophthalein test returned earlier to normal than in the controls, and the patients could be discharged two weeks earlier than controls. Biopsies revealed a more rapid return toward normalcy than the controls, but fatty changes were even more conspicuous than in the corticotropin-treated group. Two patients had relapses, and this feature diluted the otherwise favorable evaluation. It is of interest that administration of globulin [47] did not prevent relapses. Sborov et al.[48] studied 49 patients treated with various schedules of corticotropin. The mean duration of abnormal tests was shorter than in controls, but differences between test cases and controls were minor and not significant statistically. The differences observed in serial biopsies, performed at 10-day intervals, were not clear-cut. The authors concluded that more experience is needed before definite conclusions as to the therapeutic benefits of corticotropin may be drawn. Ducci and Katz [49] studied the effect of cortisone on infectious hepatitis with adequate controls. There was a pronounced fall in the serum bilirubin and a striking improvement in the sense of well-being. The results, nevertheless, had such a magnitude in the standard deviation that 800 patients would be required for adequate statistical evaluation, instead of the 32 patients. No differences were observed in the flocculation tests, and fatty infiltration was not observed in biopsy specimens. Johnson and Bennett [50] studied 22 patients treated with corticotropin intravenously, as compared with 32 controls, and concluded that corticotropin has no place in the usual acute hepatitis. Heilmeyer et al.[51] also compared 30 patients treated with cortisone and cortisone with 100 controls of a comparable age and sex and with a comparable initial serum bilirubin level. In the treated patients there was a more rapid decline in serum bilirubin and a statistically significant shortening of the disease (if a serum bilirubin of 1 to 2 mg. % was considered the end-point of the disease process, a rather dubious assumption). Corticotropin and cortisone were considered by the authors to be useful in the management of infectious hepatitis. There also were signs of improvement in the histological picture on serial biopsies, consisting in less cellular infiltration. Kirkeby et al.[52] treated 38 patients with infectious hepatitis with corticotropin. Again, there was an impressive fall in the icterus index, a rise in the depressed prothrombin level, and general clinical improvement; no controls were studied. The authors felt this treatment was beneficial, probably through suppression of inflammatory phe-

nomena in the liver. Four relapses occurred, attributable to premature withdrawal of medication; no side-effects were observed. Huber and Wiley[53] studied 100 patients with hepatitis and a comparable group of controls. The results were a more rapid clearing of jaundice, speedier return of appetite, a greater increase of effective body weight, and an earlier return of the sulfobromophthalein test to normal. The authors recommended cortisone for hepatitis, not responding to conventional measures. Caroli and Delattre,[54] impressed by favorable results with steroids in all types of hepatitis, acute and prolonged, and by the low incidence of side-effects, advocate these agents early in the course of hepatitis, mild and severe. Nelson,[55] on the other hand, would reserve cortisone for severe acute hepatitis. The criteria to be observed are a bilirubin level exceeding 15 mg. %; uncontrollable nausea; vomiting, and evidence of hepatic necrosis, as shown by a disturbed sensorium, by a rapidly shrinking liver, or by coma. In a recent report by Ducci et al.,[56] cortisone was given to 41 patients for nine days. Four relapses occurred. The author recommends steroids for severe and fulminant cases only. From this summary, it seems clear that corticotropin and steroids are helpful in severe and fulminant hepatitis. The advantages of such treatment in mild forms of disease are not evident, and although some would recommend their use generally, most observers would limit corticotropin and the adrenal steroids to selected cases with an apparently serious prognosis.

Corticotropin and Steroids in Chronic Hepatitis

Chronic hepatitis is a potpourri of many clinical syndromes and may encompass hepatitis with a more protracted course to cholangiolitic hepatitis, while others would include hepatitis associated with endocrinological disturbances. Many patients are asymptomatic and thus remain undiagnosed. It would be difficult, therefore, to evaluate data from the literature dealing with differing clinical and pathological entities. Only a few interesting reports will be mentioned. According to Holmes and Percefull,[57] hepatic-function tests and biopsies in two patients with protracted posthepatitic jaundice did not change. It is important to mention that careful studies of liver function in 23 normal persons did not reveal any changes after the administration of cortisone, in contrast to findings in rabbits given cortisone.[58] Saint et al.[59] described 34 cases of chronic hepatitis presenting histologically inflammatory infiltrates in the mesenchymal tissue. Five additional cases had residual fibrosis and were defined as inactive. Their experience with corticotropin was limited, and the results obtained were equivocal. Lebon and Gelin,[60] in Algiers, reported satisfactory results in seven patients with protracted jaundice treated with cortisone and also in a case complicated by glomerulonephritis. Surprisingly, control biopsies of the liver repeatedly gave evidence of cure. This observation raises the question of variability in the histological appearance of a chance biopsy specimen and of variability of clinical material in different geographical areas. Last[61] treated nine cases of active chronic infectious hepatitis with corticotropin and cortisone, with apparent clinical improvement in eight patients. In repeated biopsies the histological picture was unchanged, and examination of the liver at autopsy in three cases also indicated that steroids do not influence the histopathological features of the disease process. McHardy et al.[62] concluded that the limitations of other therapy in chronic viral hepatitis justify the "heroic trial" of corticotropin and corticosteroids.

Demeulenaere and Vermeulen[63] treated 12 patients with chronic parenchymatous hepatitis with steroids. In 10 cases the "biological evolution" of the disease was uninfluenced; the general condition of the patients, nevertheless, appeared improved. Sborov et al.[75] treated 18 patients with chronic liver disease with corticotropin, cortisone, or a combination of both; 8 pa-

tients had a sustained improvement, both clinically and biochemically. Liver biopsies, nevertheless, failed to demonstrate improvement. Seven patients did not benefit from corticoid therapy. In two patients there was progression to coma and death. The remaining patient had two relapses on withdrawal of cortisone.

In summary, the limited experience in the confused field of chronic hepatitis indicates that clinical improvement may occur during corticotropin and/or steroid treatment; liver-function tests may improve, but the histological findings do not seem to lessen; the basic tissue reaction in chronic hepatitis probably remains unchanged.

Corticotropin and Steroids in Cirrhosis of the Liver

Initially, adrenocortical therapy was applied with the hope of lessening the fibrosis; the inflammatory infiltration, frequent accompaniment of liver cirrhosis, also might be decreased. Hanger and Collins,[64] in two cases of coarse nodular cirrhosis treated with cortisone, noted a reduction in the size of the liver and a decrease in the inflammatory reaction; the appearance of the hepatic cells, bile ducts, or Kupffer cells was unchanged. Flink and Williams[65] treated five patients with corticotropin; no benefit was observed; there was no significant change in liver-function tests; two patients developed ascites, and one died of hemorrhage from esophageal varices. Bongiovanni et al.,[66] did not observe significant improvement during treatment for periods of 6 to 21 days. Brown et al.,[67] in four patients treated with corticotropin, reported pronounced increase in appetite; two patients had an increase in hemoglobin and hematocrit; the impression was that corticotropin has no deleterious effects upon the liver and seems of value in the treatment of cirrhosis. Havens and others[68] treated 15 patients with cirrhosis with various schedules of corticotropin and cortisone. Liver function remained generally unmodified. More than half of the treated patients developed edema and ascites, even when the salt intake was reduced to 300 mg. per day. Halsted[69] did not observe improvement in two patients with Laennec's cirrhosis treated with cortisone. Cachera and Darnis,[70] in a careful biochemical and histological study of three cases of portal cirrhosis, concluded that Laennec's cirrhosis apparently is accompanied by hypersecretion of corticoids of the aldosterone type and not of the cortisone type; the latter, therefore, cannot be considered as replacement therapy. The amount of fat in the liver may be reduced, but fibrotic changes persist; there is only a slight reduction in the amount of inflammatory cells.

Chapman et al.[71] administered 100 mg. of cortisone a day for 18 days to three patients with Laennec's cirrhosis on a low-sodium regimen. The livers became larger and more firm in consistency. There was an increase in plasma albumin and a decrease in the globulins. In one case diuresis increased greatly in the later phase of treatment; this diuretic effect was consistent and significant. However, the clinical and metabolic changes were not permanent, and two weeks after discontinuance of therapy, the effects of steroid treatment had subsided. Blahd and others[72] studied six patients with cirrhosis and three normal controls with respect to electrolyte responses during the use of corticotropin, cortisone, and deoxycorticosterone. Patients with compensated cirrhosis responded like normals, with sodium retention when the drugs were used singly or in combination. In advanced decompensated cirrhosis there was no response to corticotropin or steroids, due perhaps to a maximum effect of salt-retaining steroids on renal tubules. In compensated cases withdrawal of drug resulted in increased diuresis, with disappearance of edema and ascites. Suzman[44] observed, in two patients with cirrhosis and jaundice, a temporary decrease in the serum bilirubin level, with a rebound when the medication was discontinued. There was no change in liver function or in the histological appearance of the liver.

Zoeckler [73] performed a controlled study of 36 patients with portal cirrhosis; half of them with ascites. The cortisone-treated had a significant rise in serum albumin. No difference was found between treated and controls with regard to sulfobromophthalein test, serum bilirubin, alkaline phosphatase, or thymol turbidity determination; cephalin-flocculation tests were abnormal in all patients prior to treatment, but four of nine had normal flocculation tests after treatment. There was less fat in biopsy specimens of the treated group after treatment than previously. There was no difference in the degree of inflammatory infiltration in both groups. The conclusion, nevertheless, was that cortisone has a definite place in the treatment of portal cirrhosis. Remolar [74] studied the histopathology of liver cirrhosis before and after intravenous infusions of corticotropin in 13 patients. After corticotropin there was a neater and uniform distribution of the chondriome in liver cells. There was a slight decrease or no change in the amount of fat. A moderate increase and a uniform distribution of mucopolysaccharides was observed. This therapy would be indicated only in early fibrosis but does not seem justified for frank cirrhosis. Sborov et al.[75] had studied nine patients with cirrhosis treated with corticotropin or cortisone or both. There was some improvement in the sense of well-being and in liver function in four patients. The course of the disease was unaffected in four cases. In one patient severe ascites supervened, with bleeding from esophageal varices. The over-all results from corticotropin and cortisone in treatment of liver cirrhosis were rather disappointing, and the increase of edema and ascites made their use undesirable. The development of glucosteroids with less mineral-corticoid effects has renewed interest in the steroid treatment of liver cirrhosis.[76] Bariety et al.[77] studied the effect of prednisone in 5 cirrhotic patients and in 13 normal subjects. In three of five patients there was a significant rise in sodium excretion, with diuresis. The advanced cases, with poor diuresis initially, did not attain as good results. Winkler and Tygstrup [78] studied six cases of liver cirrhosis with edema and ascites treated with prednisone. Two patients died; in one the drug was only slightly effective, and in three the effects again were nonspecific, consisting of an improved appetite and sense of well-being, disappearance of fever, etc. Wildhirt [79] treated 28 cases of liver cirrhosis with prednisone and prenisolone over a period of two weeks. There was an increase in the albumin-globulin ratio and a decrease in the inflammatory activity, as noted in liver biopsy specimens. The beneficial influence was considered favorable in 13 cases and slight in 5. No change was present in nine, and decline occurred in one patient. The author considers these agents very important adjuncts in the management of liver cirrhosis. Beltrametti and Levi [80] treated 17 patients with liver cirrhosis and ascites with prednisone. In 10 patients there was increased diuresis with weight loss; less pronounced diuretic action was noticed in 3 and no response in 4 cases. The authors' interpretation of the therapeutic effect was increased glomerular filtration, decreased tubular absorption, and diminution in the adrenocortical hypersecretion of aldosterone.

Muller et al.[81] treated 22 patients with liver cirrhosis with prednisone, 20 to 30 mg. per day, for periods up to four months. There was a favorable influence on the jaundice, appetite, sense of well-being, and diuresis; liver function remained unchanged. Three patients died—one in coma and another because of intercurrent infection, and a third died six weeks after discontinuance of therapy. The diuretic effect was defined as spectacular and fully justified use of the drug. De Gennes et al.[82] similarly treated 32 patients with alcoholic cirrhosis and ascites and noted no benefit when the liver was small. In 25 cases of so-called hypertrophic cirrhosis there was polyuria, natriuria, and lessening of the ascites. Sixteen patients improved for periods up to 12 months. These authors recommend prednisone for six weeks only and consider more

prolonged therapy unwarranted. Vachon et al.[83] treated 24 patients with alcoholic cirrhosis and ascites with prednisone for periods of one to two months. Again, there was a remarkable diuretic effect continuing in 11 of 18 cases; no side-effects were observed. The authors consider prednisone highly useful in patients with ascites and edema; nevertheless, they admit that the basic cirrhotic process seems uninfluenced. Lamache et al.[84] treated 29 patients similarly; their report is of interest because of detailed histopathological studies. The amount of fibrosis in the serial biopsy specimens remained unchanged; fatty infiltration present in 24 of 29 patients appeared reduced on repeat biopsy in 15 of 24 patients. In four cases there was an increase in fat or fat appeared, not having been observed in a previous biopsy. There was diminution of the inflammatory infiltrate in 10 of 24 cases and persistence of the same amount of infiltrate in 8 observations. In three cases the pronounced cellular infiltration reappeared after initial diminution on steroid therapy. The authors recommend a brief course of steroid therapy in alcoholic cirrhosis.

In a recent report[85] of nine cases of postnecrotic cirrhosis attributed to anicteric infectious hepatitis, corticotropin and steroids were used in three patients. In one case, corticotropin was administered for two weeks and repeated biopsies indicated reduction of the inflammatory exudate. The hepatic trabeculae seemed more compact, and the collagen bundles in the fibrotic areas appeared thicker than in previous observations. In another patient corticosteroids were administered over a period of four months, with a remission of symptoms lasting eight months. In a third case corticotropin was given for four weeks; then its use was discontinued, because of epigastric distress suggestive of peptic ulcer. The author considers prolonged steroid treatment beneficial if instituted early in the icteric cases of subacute liver necrosis. In summary, the benefits derived from steroid therapy are of a general nature and apparently do not influence the basic disease. The diuretic effect in some of the cortisone-treated patients is enhanced considerably with the newer synthetic steroid derivatives. Nevertheless, it is obvious that the ultimate role of steroids in liver cirrhosis must be studied in relation to the survival rate of treated and untreated cases and in larger groups of patients before final conclusions are warranted.

Corticotropin and Steroids in Hepatic Coma and Precoma

Hepatic coma may occur as an expression of hepatic failure in fulminating or subacute hepatitis or may represent a terminal event in liver cirrhosis. Eppinger[86] first suggested the use of adrenal cortical extract in severe acute hepatitis, based on the assumption that it might correct a presumed state of adrenal cortical insufficiency. The use of such extracts was very slow, since Thorling,[87] in 1950, reported a series of cases of infectious hepatitis with neurological manifestations and expressed the hope that corticoids might improve the poor prognosis of these conditions. Frey[88] administered extract "Percortenglukosid" (which, to the author's knowledge, contained glucosteroids and other hormones of the adrenal cortex); two cases of acute hepatitis, one patient in precoma, improved. Webster[89] reported nine patients with various liver diseases treated with aqueous or oil adrenocortical extract; four were semicomatose or drowsy and improved. The author was aware of the fact that pure agents, when obtained, might be of greater value, but considered it worth while to treat the patients with the extracts then available.

Ducci[90] described recovery from fulminating infectious hepatitis with deep coma following intramuscular injection of cortisone up to 200 mg. a day. This response had been unusual in the author's experience of more than 1,000 cases of infectious hepatitis. Failures with steroid therapy also have been reported.[91] Sherlock[92] treated six patients in coma from acute hepatitis with intravenous infusions of hydrocortisone,

400 mg. daily; four patients died, and two recovered; the impression was that steroid treatment might "buy time" to allow the severely damaged liver to regenerate. In our experience,[93] intravenous hydrocortisone did not influence the course of a patient with a subacute fatal hepatitis, who died in coma. Others,[94-96] following Ducci, were impressed with dramatic improvements in patients with confusion and coma in the course of acute hepatitis. The study of 11 cases of severe and fulminating hepatitis by Evans et al.[97] is of interest. If the five patients who recovered were compared to those not treated with corticotropin or steroids, it became obvious that corticotropin and corticoids did not accelerate recovery from the illness if a normal sulfobromophalein test and a normal serum bilirubin were considered the expression for such recovery. With intervening coma the outcome was death, and none showed any clinical response. Later, one patient was observed to recover from coma, following the injection of 1,000 mg. cortisone daily.

With regard to coma complicating severe hepatic cirrhosis, results remain variable and unpredictable. Williams and Flink[98] observed in liver cirrhosis and in a patient with a common bile duct stricture, a minor decrease in serum bilirubin, but a significant decline in bile acids, with relief of pruritus. Administration of corticotropin did not prevent the patient from lapsing into stupor or coma on three occasions. Zoeckler and Hegstrom[99] treated seven patients with cortisone and noted clinical and histological improvement in five. Cortisone brought patients out of precomatous lethargy on three occasions but did not prevent death in two patients after a brief coma. Alexander and Porter[100] reported a case of cirrhosis with coma not responding to an infusion of 23 gm. of sodium glutamate who awoke from deep coma on the third day of corticotropin administration. Sklar and Young[101] described 10 cases of advanced portal cirrhosis treated with intramuscular injection of repository corticotropin injection (ACTH Gel); five were in coma at the start of treatment and failed to respond; three were in impending coma, and two were clear but lapsed into coma during therapy; these patients also received other medication and a diet containing 100 gm. of protein. Sborov et al.[75] observed a definite but transitory response of two comatose patients to corticotropin. Webster and Davidson[102] studied seven patients with coma or impending coma. Four improved temporarily, but all eventually died. The blood ammonia decreased in the four who improved. Such a temporary improvement with a perfectly lucid interval also has been observed by others.[93] Spellberg[103,104] treated seven patients with large doses of corticotropin and/or hydrocortisone intravenously. Five died, and two were "rescued" from coma on two separate occasions. There seemed to be a relationship between the dose of corticotropin and the clearing of the sensorium. In a large study[105] of 63 patients with hepatic coma treated with cortisone and hydrocortisone there was no additional benefit from these agents. This study was directed mainly at the role of proteins in coma, and a controlled study of such a group of patients with respect to steroids might have given more information on the role and mechanism of action of steroids.

Corticotropin and Steroids in Cholangiolitic Hepatitis and Cholangiolitic Cirrhosis

Cholangiolitic hepatitis is a clinical syndrome of varied etiology, representing probably one of the patterns of the liver in response to injury.[106] Attention has been focused on this syndrome by Watson and Hoffbauer,[107] and three of their cases exemplified the transition from hepatitis into cirrhosis. Increased cholangiolar permeability was assumed to be the basic lesion in the acute disease; such abnormality might be expected theoretically to be amenable to steroid therapy. Interest in cholangiolitic hepatitis has increased recently because of the many cases observed in conjuntion with the use of cholopromazine and other drugs.[108] The drug-induced hepatitis usually

is an acute and reversible form, but cases with prolonged illness merging into biliary cirrhosis with or without xanthomata have been observed.[109] Williams and Flink[98] observed a fall in the level of bile acids in the blood of two patients with cholangiolitic cirrhosis treated with corticotropin; relief from pruritus also was observed. Nevertheless, no sustained benefit resulted from such treatment. In the classical paper by Ahrens et al.,[110] one patient with biliary cirrhosis is mentioned who received corticotropin, without benefit. Sborov et al.[48] treated six patients with cholangiolitic hepatitis with corticotropin, with remarkable clinical improvement. Carman and Giansiracusa[111] undertook prolonged therapy with corticotropin and hydrocortisone in a patient with primary biliary cirrhosis. On three occasions improvement, both clinical and biochemical, was observed with such consistency and rapidity that the possibility of a spontaneous variation seemed unlikely. The liver and spleen decreased in size, and the alkaline phosphatase declined to near normal values; the serum bilirubin and serum lipids declined in parallel fashion. Lipschutz and Capson[112] discussed the theoretical value of steroid therapy for cholangiolitic hepatitis, basing their conclusions on analogies with the nephrotic syndrome. Johnson and Doenges[113] described two cases of cholangiolitic hepatitis, improving remarkably on intravenous corticotropin. MacPhee[114] used cortisone 50 mg. daily for four months in two cases of primary biliary cirrhosis with the pupose of arresting the progressive perilobular fibrosis; the results were unimpressive. Albot[115] considers corticotropin and steroids of little value in the usual variety of cholangiolitic hepatitis. The general condition of the patients may improve, but liver function and the histologic changes do not improve significantly. A variant of this disease, diffuse mesenchymal hepatitis with lymphomatous nodules, responds to steroid treatment with complete clinical, biochemical, and histological remission. This disease, however, is extremely rare, and only a few cases have been reported. Cutts[116] reported good results with cortisone in a case of chlorpromazine jaundice. Stein and Wright[117] similarly described dramatic clearing of jaundice during the administration of 75 mg. of cortisone a day. Elliott et al.[118] observed in an acutely ill patient a prompt cessation of vomiting and decline of bilirubin level; the bilirubin rose when the drug was decreased prematurely. Hollister[119] concluded, nevertheless, on the basis of a study of 17 patients with chlorpromazine jaundice, "No proof exists that steroids altered the natural course of the illness." Kühn et al[120] reported three instances of primary biliary cirrhosis in women in the fifth decade of life, with jaundice and pruritus of several years' duration. In one case cortisone did not seem helpful; in another, both corticotropin and cortisone did not influence the fatal course of the disease. Summerskill[121] recorded four patients with cholangiolitic hepatitis who were benefited by steroid therapy. Wilson et al.[122] treated six patients with xanthomatous biliary cirrhosis with prolonged courses of prednisone and cortisone. The biochemical response included a decline in serum bilirubin, alkaline phosphatase, thymol turbidity, total phospholipids, and cholesterol. In our experience,[93] cholesterol, unlike alkaline phosphatase, continued to rise during the administration of steroids. Repeated biopsies[93] did not show significant changes, and our conclusion was that steroids may produce clinical improvement but the basic disease does not seem to be influenced favorably.

Chronic Liver Disease of Possible Immunological Origin

Allergic phenomena of the liver are considered medical rarities. This should be surprising, since the liver constitutes the first station to which degradation products of proteins arrive from the intestine. The rarity in the diagnosis of hypersensitive states of the liver probably is related to the inadequacy of our methods.[123] It seems safe to conclude[123] that the liver may be the site

of "hyperimmune disease" or that it may participate in hypersensitivity phenomena occurring elsewhere in the organism. However, in the absence of conclusive evidence of an antigen-antibody relationship with action site in the liver, the diagnosis of such states is only presumptive. With this limitation, it is of interest to review the known effects of corticotropin and steroids in such conditions.

To this category of liver disease probably belong the cases described in 1950 by Waldenström.[124] These were young women with progressive liver disease and signs of endocrine disturbances. They had characteristically a very high plasma gamma globulin with a broad-base electrophoretic peak. "Striking" improvement on corticotropin treatment was observed. A larger group of young women was reported by Bearn et al.[125] There was in these cases, also, a pronounced and persistent improvement on cortisone, with clinical and biochemical relapse when cortisone was withdrawn. Mackay et al.[126] called attention to a similar group of patients, mostly young women who had had a positive L. E. test and severe hepatic disease. Cortisone produced remissions in most of them. The presence of L. E. cells was interpreted as evidence of antibodies to leukocytes and suggested to the authors that the hepatitis might have resulted from antigen-antibody interaction. This theory would coincide with the concepts of Burnet and Fenner[127] and of Gear.[128] L. E. cells also have been found by others in chronic liver disease without necessarily signifying coexisting disseminated lupus erythematosus.[93,125,126,129,130]

In the last few years, the concept of autoimmune mechanisms of certain human diseases has gained support. To cite a few examples: certain hematological disorders with acquired hemolytic features and certain forms of chronic thyroid disorders. The theory of "horror autotoxicus" formulated by Ehrlich[131] is still well accepted, and convincing evidence will have to be submitted before autoimmune mechanisms will enter as an important part of human pathology. One possible approach is that of Gajdusek,[132] who used human tissue antigens, and particularly human liver, for complement-fixation tests. In normal persons and in a variety of conditions, there was no complement fixation. In disseminated lupus erythematosus and in the so-called lupoid hepatitis there was a positive complement-fixation test in 75% of cases, mostly at a titer above 1:16. This was interpreted as evidence of antibodies against proteins of human tissue. Such proteins could possibly become antigenic by chemical, viral, or toxic influences. This explanation is corroborated by the fact that human liver tissue injected into rabbits, guinea pigs, and rats provoked a high titer complement-fixation response. It is, nevertheless, noteworthy that even in cases with a high complement-fixation titer, the serum of the patients fail to react with the patient's own organs.[133] These studies recently have been extended.[134,135] Strikingly high titers were observed in a patient with nonobstructive biliary cirrhosis.[136] In this case, too, prednisolone caused subjective improvement and gain in strength but had no influence on the hepatomegaly or the lipid deposits. We also[137] noted recently a striking remission on prednisone therapy in a young woman with hepatosplenomegaly, anemia, severe uveitis, and high plasma γ-globulins. Bartholomew et al.[138] recently described seven cases, mostly young women with symptoms both of disseminated lupus erythematosus and severe liver disease; in one there was recurrence of symptoms despite cortisone therapy, and in another, prolonged steroid treatment preceded evidence of severe liver disease. Although some studies[139] would suggest that disseminated lupus erythematosus results from sensitization against intrinsic or extrinsic nucleoproteins, the cases described by Bartholomew and others seem to differ from those of previous authors.[124-126] Knowledge of this group of disorders is fragmentary, but the beneficial effects of corticotropin and the adrenal

steroids upon their course seem more consistent than in other types of liver disease.

Corticotropin and Steroids in Gilbert's Disease

Constitutional hepatic dysfunction of the type described by Gilbert et al.[140] is a benign disease characterized by jaundice with an elevated indirect-reacting bilirubin. Obstruction or hemolysis is not present, and the morphology of the liver seems normal. The mechanism of the disturbance may be a conjugation defect or diminished permeability of the hepatic cells. The disease is benign and requires no treatment. It is of interest, nevertheless, to report several observations on the effect of steroids in this disease. Chalmers et al.[28] found a slight depression of serum bilirubin in patients with Gilbert's disease given corticotropin. Eanet and Brick [141] observed no significant alteration in serum bilirubin in a patient given corticotropin or cortisone. McMahon [142] did not observe any effect from prednisolone on bilirubin levels in the hyperbilirubinemia induced at will by physical exertion in a patient with constitutional hepatic dysfunction.

Corticotropin and Steroids in Dubin-Johnson Syndrome

This chronic disease characterized by a nonhemolytic jaundice has been described only recently.[143] Bile appears intermittently in the urine; increased sulfobromophthalein retention is common. The gallbladder ordinarily does not visualize. Symptoms are mild and intermittent. The diagnosis is made by the demonstration of a characteristic pigment in liver cells in biopsy specimens. A case has been described [144] of a 21-year-old man with signs and symptoms of this disease. Corticotropin did not change the bilirubin level or the excretion of fecal and urinary urobilinogen. The dark biopsy specimen of liver obtained by needle during corticotropin treatment did not differ from that taken before the drug was administered.

Corticotropin and Steroids in Wilson's Disease

Hepatolenticular degeneration, or Wilson's disease, is a chronic condition characterized by increased absorption of copper with accumulation of this metal in tissues. Heavy deposition in the liver causes liver cirrhosis. Accumulation of the metal in the basal ganglia will produce cavitation and neurological symptoms. The most characteristic features of this disease are reduction of blood ceruloplasmin and increase in urinary excretion of copper, amino acids, peptides, and glucose. Bearn and Kunkel [145] observed a positive correlation between urinary excretion of copper and amino acids. Since amino acids rise sharply under corticotropin administration,[146] it was expected that steroids will promote an increased excretion of both. Bearn and Kunkel,[145] indeed, made such an observation. Gilsanz et al.[147] could not confirm these results. Patients given corticotropin had an increased excretion in the total nitrogen and in the amino nitrogen as well, while excretion of copper remained unaltered. Dimercaprol, on the contrary, promoted a copious excretion of copper, while the amino acids remained unaltered. These are isolated observations, and corticotropin and steroids do not appear to have any significant therapeutic benefit in Wilson's disease.

Comment

Discussion of the role of corticotropin and steroids in liver disease should include both the hazards and the advantages of such therapy. The complications and side-effects of corticotropin and steroid therapy are well known. Diabetes may appear in predisposed persons; it usually is transitory and of no major concern, especially in view of the short-term steroid therapy applied in liver disease. Water and electrolyte imbalance is particularly noticeable when patients with cirrhosis with or without ascites are treated with corticotropin or cortisone. The use of prednisone and pred-

nisolone corrected this defect of cortisone therapy and permitted the observation of the effect of the former in liver cirrhosis on large numbers of patients. Cushingoid features were observed in some cases but did not seem to be a major problem. Psychiatric complications were unusual. Intercurrent infection has been rarely observed.[81] Perforation of a peptic ulcer has been reported only once [44] in the literature reviewed. The rise in blood pressure and the increased hydremia could represent a potential danger for the rupture of esophageal varices. Butt et al.[148] clearly alluded to this hazard while discussing the sequence of varices ruptured, hemorrhage, coma, and death in a patient with cirrhosis after homologous serum jaundice. Actually, gastrointestinal hemorrhage as a complication of steroid therapy has been rare [44] in the literature reviewed and ruptured varices infrequent.[65,75] Thrombosis during corticotropin and steroid treatment also deserves some consideration. Eisenmenger et al.[149] observed three instances of portal vein thrombosis in patients with cirrhosis during the administration of corticotropin. The authors, therefore, carefully studied the various components of the coagulation mechanism and found the antithrombin activity reduced in most cases. While prothrombin levels and the number of platelets remained unchanged, the hypercoagulability of the blood could be corrected by the administration of heparin. Smith et al.[150] administered corticotropin to three normal subjects and observed an increase in heparin-like substances, with prolongation of the clotting time. In 20 patients with various diseases similarly treated there were changes on corticotropin and cortisone therapy, which varied from patient to patient. No broad conclusions could be drawn as to the effect of the treatment on the coagulation mechanism. Cosgriff [151] observed 28 instances of thromboembolic phenomena in 700 patients treated with corticotropin or cortisone. Cosgriff et al.[152] subsequently studied blood coagulation prior to, at the time of, and after treatment. Eight of ten patients had shortening of the venous coagulation time, while two patients had no change. There was no alteration in prothrombin level or in protamine titration; resistance to bishydroxycoumarin (Dicumarol) did not develop during such treatment. Even if hypercoagulability seems to be a possibility in steroid therapy, the cases reported by Eisenmenger et al.[149] remain unusual. Portal vein thrombosis has been observed frequently in cirrhosis of the liver in the absence of steroid treatment, and one wonders if the three cases do not illustrate a fortuitous occurrence.

The most commonly observed effects of corticotropin and steroids on the clinical course of liver disease are an increased appetite and a decrease in the serum bilirubin.* The mechanism of the steroid action on the bilirubin level has been discussed in a previous section. It is also significant that, contrary to the usual variability in biological phenomena, there never has been reported increased jaundice during steroid treatment. Improvement in the sense of well-being is a common occurrence and certainly is not characteristic of hepatic disease alone. These features of decreased jaundice, increased appetite, and sense of well-being tended to be persistent after discontinuance of therapy. In acute hepatitis only were relapses observed [41,42,45,46,52,56] sometimes responsive to the resumption of therapy. Relapses are unusual in the course of acute viral hepatitis, and steroid treatment, therefore, has been reserved for severe and fulminant cases.

The role of the adrenal glands in fat metabolism and fat deposition in the liver has been mentioned. The case report of fatty infiltration of the liver on cortisone treatment is frequently quoted.[153] This could be a potential danger of steroid treatment, since fat in the liver has been shown to have a cirrhogenic effect per se. This problem, therefore, deserves closer examination. Corticotropin has been found to cause increased lipemia and fatty infiltration of the liver in rabbits.[154] The same phenomenon

* References 40-46, 49, 51, 53, 81, 111, 122.

has been reproduced in mice,[152] and mice developed a fatty liver even when exposed to a lower temperature or exercise. Other types of stress, on the contrary, were associated with disappearance of liver fat.[155] Intravenous administration of dextrose during periods of stress prevented fat deposition in the liver. Selye[156] did not observe fatty livers in animals treated with cortisone. Giraud et al.[157] observed disappearance of fat from the liver on serial biopsies of patients with fatty liver during steroid treatment. No increase in fat has been observed in cases of chronic cholangiolitic hepatitis treated with prednisone (Meticorten).[93] The fat in the liver has been found to be diminished in the majority of observations,[38,39,70,73,74,84] while an increase in fat under steroid therapy has been reported less frequently.[45,46,84]

It has been noted[158,159] that bilateral adrenalectomy in partially hepatectomized rats prevents increase of the size of the liver remnant. Administration of cortical extracts would return the function of protein formation and multiplication of hepatic cells. One would expect a more lively regeneration in liver cirrhosis under steroid treatment, since regeneration is an essential part of the cirrhotic process. It is surprising, therefore, not to have found observations on increase in size of liver nodules; the short-term treatment applied in cirrhosis may explain the lack of such observations.

The histology of the hepatic cells under steroid treatment has been described by different observers.[74,84] The influence seemed to be favorable, since cells were described as more "neat" and of a more uniform distribution of particulate matter in the protoplasm. In reality, steroids may cause very complex changes in the liver cells. Lowe and Williams[160] observed, for instance, an increase in the soluble ribonucleic acid under steroid treatment; on histological sections it was evidenced by loss of liver-cell basophilia. Since cytochrome systems function in relation to particulate ribonucleic acid, such systems may be inhibited in their function when corticotropin and steroids are administered. On the other hand, adrenalectomy was found[161] to reduce cytochrome C in the liver, whereas administration of adrenal cortical extract restored the cytochrome C. The role of steroids, therefore, seems complex, and, for as yet unknown reasons, their actions may appear to be in diametrically opposed directions.

Is there any evidence that corticosteroids may reduce the amount of fibrosis present in the liver? Such an occurrence would not be unreasonable, since such an observation has been made in the experimental cirrhosis of animals.[162] No reports of lessened fibrosis in liver biopsy specimens were found in the reviewed literature. Control biopsies have confirmed an equal amount of fibrosis as in preceding biopsies on many occasions.[44,70,73,83,84] Therefore, once established, fibrosis of the liver does not seem to be affected by corticotropin and corticosteroid therapy.

A final comment on the necessity of controlled studies on statistically significant numbers of patients. Most of the reports cited in this review have been based on clinical impressions of small groups of patients. A more scientific approach was used in the treatment of acute hepatitis, but, nevertheless, statistical significance has been lacking. The data of Ducci and Katz[49] may be illustrative; their series comprised 32 cases; yet for statistical significance as many as 800 would have been necessary. Webster,[89] for instance, was impressed with good results obtained with adrenal cortical extracts, but when a critical study[162] was made of such therapy in hepatitis no "substantial superiority" was found in this type of treatment when compared with adequate controls.

Summary

Corticotropin (ACTH) and corticosteroids seem to differ in their pharmacological effects in relation to the species of animal and to the dosage used. They inhibit the inflammatory reaction, the fibroblastic proliferation, capillary budding, and granuloma

formation. They decrease capillary permeability and seem to diminish immunological responses.

In relation to the liver they cause a marked increase in glycogen and in protein content. Fat may or may not be increased in the liver of animals treated with these agents. Steroids have been found to prevent hepatic necrosis, reduce the amount of reticulum, and reverse experimentally induced cirrhosis.

By far, the most outstanding feature of steroids in liver disease is reduction of the serum bilirubin in jaundiced patients. This may be the result of their unspecific antiphlogistic action; it may be facilitated by decrease of cellular permeability, by inhibition of bilirubin formation, or by reduction of inflammatory exudate around the delicate structures of the canals of Hering.

In infectious hepatitis, the unusual number of relapses seems to preclude treatment in the usual form of this disease. Although many patients have been studied, the data lack statistical significance. Corticotropin and the adrenal steroids have a favorable effect on the symptoms of the disease; they seem to shorten the duration of the illness when given after 10 days after start of symptoms, but the general experience indicates that these drugs should be reserved for the severe and fulminant cases. Corticotropin and steroid treatment appear to have little or no advantage in chronic active hepatitis.

Corticotropin and steroids produce symptomatic improvement in patients with cirrhosis of the liver, with and without jaundice, with and without ascites. They may decrease the level of bile acid in the serum with lessening of the pruritus. There may be an increase in appetite and in the sense of well-being, increase in blood plasma albumin, decrease in globulin, and decrease in fat in tissue biopsy. In approximately half of the patients corticotropin and cortisone increase salt and water retention and intensify the ascites. The newer analogues, prednisone and prednisolone, seem to be less troublesome in this respect. However, the basic process of liver cirrhosis remains unaffected, and in no case did the cirrhotic process appear to be reversed.

Hepatic coma has been characterized clinically by occasional spectacular recoveries and by more frequent failures. There exists a form of hepatic coma dependent upon "exogenous" nitrogen which appears reversible. Since in a given case the type of coma is not always evident, clinical evaluation probably concerns different conditions with similar manifestations but with varying prognoses.

In cholangiolitic hepatitis, the improvement might be attributed to the usual nonspecific action of steroids in the jaundiced patient. The basic process seems unaffected.

There appears to be more agreement as to the favorable results of corticotropin and steroids on liver disease of immunological origin. However, the available information appears to be scanty.

There is no evidence that corticotropin and steroids are of value in the treatment of disorders of the liver such as Gilbert's disease, the Dubin-Johnson syndrome, or the hepatic disease associated with hepatolenticular degeneration.

Conclusions

1. The literature contains a noticeable lack of adverse effects from corticotropin and steroids in patients treated for liver disease.

2. Steroids are useful adjuncts in the symptomatic management of various diseases of the liver—especially severe acute hepatitis, cholangiolitic hepatitis, and those forms of liver disease with immunological features. Newer analogues are useful in the management of hepatic cirrhosis with ascites.

3. The basic process and the natural history of liver disease appear to be unchanged.

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News and Comment

The reprints of the following articles published as a unit on Renal Physiology will no longer be available from Baird-Ward Printing Company after September 30th.

Maurice B. Strauss	The Urine Remains the Same
F. R. Winton	Present Concepts of the Renal Circulation
David D. Thompson	Renal Excretion of Calcium and Phosphorus
Ezra Lamdin	Mechanisms of Urinary Concentration and Dilution

Evolution of Modern Medicine

This section, which has as its primary purpose a review of the contributions of medical investigators and observers of the past to the present-day concepts of disease, is under the special editorship of Dr. Arthur Bloomfield, 2398 Sacramento St., San Francisco 15.

His editorial in the August, 1957, issue of the A. M. A. Archives of Internal Medicine, *gives further detail of what it is hoped to accomplish in these articles. Contributions or comments for this section may be sent directly to Dr. Bloomfield, or to the Chief Editor for transmittal to him.*

Joseph Adams (1756-1818)

A Forgotten Founder of Medical Genetics

ARNO G. MOTULSKY, M.D., Seattle

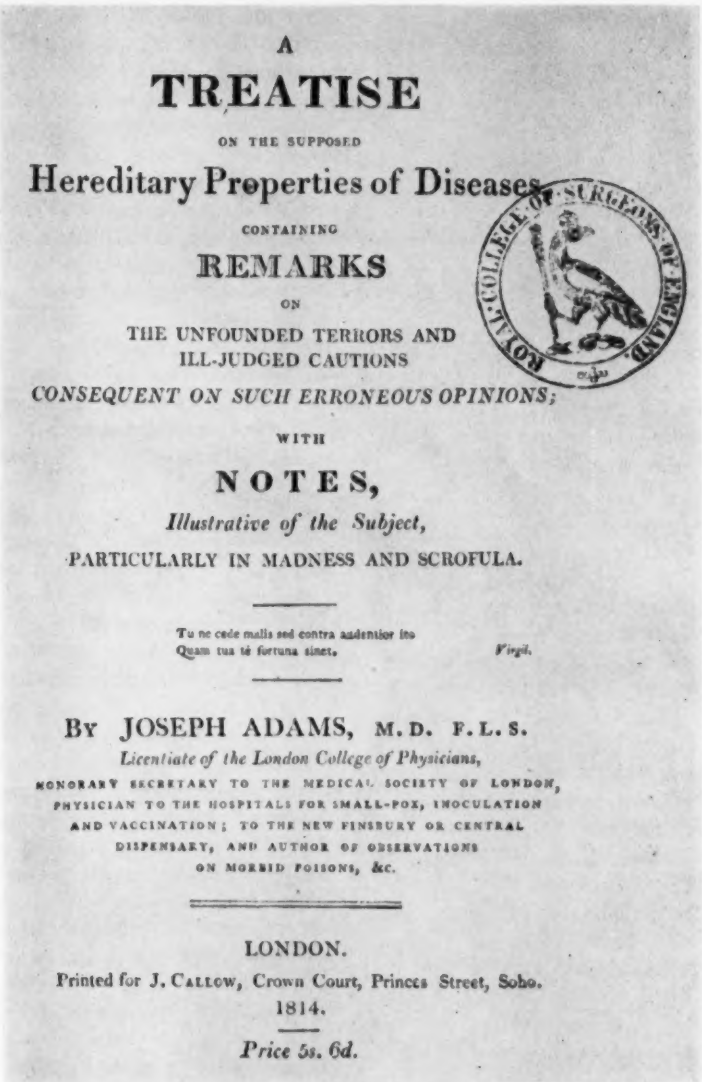
The history of human and medical genetics has roots different from those in the study of heredity in plants and animals. Likeness between human parents and offspring and between familial and hereditary diseases always intrigued scientists and physicians throughout the ages. However, few systematic accounts of hereditary diseases in man appear to have been published before the twentieth century.

Occasional brilliant insights into the principles of medical genetics already existed in early times. In 1752, Maupertuis, cited by Glass,[1] published an account of a family of polydactylia in four generations and demonstrated that the trait could be equally transmitted by father and mother. He further showed, by probability calculations, that chance alone could not account for the familial concentration of the trait. The striking sex-linked character of traits, such as color blindness and hemophilia, had also been established near the end of the eighteenth century and the beginning of the nineteenth century by various writers, such as Dalton[2] and Otto.[3] In 1808, the first edition of a short treatise by an eminent French physician appeared, entitled "Considérations sur la Nature et traitement de quelques maladies héréditaires ou de famille."[4] The author was very learned but used his terms loosely and contributed little of lasting significance. In 1814, a book entitled "A Treatise on the Supposed Hereditary Properties of Disease" was published in London[5] (Fig. 1). Its author, Joseph Adams, was at that time a fifty-six-year-old physician (Fig. 2). His book consisted of forty-one short pages of principles, followed by more extensive commentary and documentation. Adams had been a student of John Hunter, the founder of experimental surgery, whose biography he published in 1817.[6] Hunter had impressed the young man with the necessity of being direct, of avoiding abstruse language, and of backing up statements with experiments and facts. Adams, in his scientific work, never experimented or used mathematical reasoning. However, drawing on clinical experience supplemented by careful reading of many medical and scientific authors, Adams used clear thinking, brushed aside philosophical abstractions, and thus succeeded in stating many of the general principles of medical genetics which are as valid today as they were one hundred fifty years ago.

Submitted for publication May 18, 1959.

Presented in part at the meeting of the X International Congress of Genetics, Montreal, Canada, 1958.

From the Department of Medicine, University of Washington. John and Mary Markle Scholar in the Medical Sciences.



A

TREATISE

ON THE SUPPOSED

Hereditary Properties of Diseases,

CONTAINING

REMARKS

ON

THE UNFOUNDED TERRORS AND
ILL-JUDGED CAUTIONS

CONSEQUENT ON SUCH ERRONEOUS OPINIONS;

WITH

NOTES,

Illustrative of the Subject,

PARTICULARLY IN MADNESS AND SCROFULA.

Tu ne cede malis sed contra audentior ito
Quam tua te fortuna sinet. *Virgil.*

BY JOSEPH ADAMS, M.D. F.L.S.

Licentiate of the London College of Physicians,

HONORARY SECRETARY TO THE MEDICAL SOCIETY OF LONDON,
PHYSICIAN TO THE HOSPITALS FOR SMALL-POX, INOCULATION
AND VACCINATION; TO THE NEW FINSBURY OR CENTRAL
DISPENSARY, AND AUTHOR OF OBSERVATIONS
ON MORBID POISONS, &c.

LONDON.

Printed for J. CALLOW, Crown Court, Princes Street, Soho.

1814.

Price 5s. 6d.

Figure 1

Adams' aim in his book on human heredity was to provide a guide book on the inheritance of disease for genetic prognosis. "The dread of being the cause of misery to posterity has prevailed over the most laudable attachment to a beloved object. A sense of duty has opposed celibacy in those who seem by nature the best constituted for the duties of a parent! In these as in any other highly important questions, men seem afraid of inquiring after truth; cautions and cautions are multiplied to conceal the skeleton in the closet or to prevent its escape until our very fears bring the object constantly before us not in its real form but multiplied into every possible shape and magnified in all [Preface, pp. V-VI]."

Figure 2

Adams accurately distinguished between familial diseases "confined to a single generation, to brothers and sisters, the children of the same parent [p. 12]" and hereditary diseases which are "traced from generation to generation [p. 12]." He defined congenital illness as "disease appearing at birth" and pointed out that such conditions are more frequently familial rather than hereditary. At the same time, he indicated that not all congenital diseases are inherited, since contagion by morbid poisoning, such as syphilis, also might affect the newborn. Familial diseases of the inherited type, according to Adams, are often so severe (i. e., hydrocephalus) that reproduction may not occur. Thus, such diseases cannot be transmitted. But even where there was offspring, such as in deaf-mutism, he noted that children were not affected. Commenting on this fact, Adams counseled that careful distinction between familial and hereditary diseases is required, since, "By confounding heredity with familial disease we excite an unnecessary apprehension in the rising generation." Adams also pointed out that familial diseases are often confined to a single race. Arguing from this observation and from experiments with sheep where inbreeding produced bony and other deformities, he suggested, "Endemic peculiarities (in man) may be found in certain sequestered districts." By similar reasoning, he indicated that mating between near relatives would result in an increased number of patients with familial diseases. Such mating patterns, therefore, would deteriorate the race.

These are remarkable statements in 1814, and they clearly document our present-day concepts about recessively inherited disease. As Adams appreciated, such diseases are familial rather than hereditary and tend to be severer clinically than dominant diseases. Children of affected patients are free of the disease, and consanguinity increases the frequency of affected patients. In isolated districts, more cases (i. e., homozygotes) will be found because of inbreeding.

Adams recognized that minor osseous abnormalities, such as polydactylia, often are hereditary (i. e., dominant). He pointed out that an inherited disease need not be present at birth but could first manifest itself later in life. He named such a condition a susceptibility. Adams carefully subdivided susceptibility into dispositions and predispositions. A disposition is a hereditary disease occurring spontaneously at a certain age with no external cause provoking it. A predisposition needs an external factor to precipitate the illness. He indicated that certain types of blindness and deafness occurring in later life could be hereditary, while congenital privation of these senses was always confined to a single generation. With remarkable insight, Adams recognized that predisposition to an illness such as gout and "madness" might exist for several generations without clinical manifestations until a specific precipitating factor provokes the disease. "Where the predisposition exists, it is of no consequence to the future progeny whether the disease has been excited or not. For, it will sometimes be found not only that the disease has been thus excited for the first time in the family but that the progeny of the same individual will remain free from it [pp. 25-26]." Most medical

geneticists of the mid-twentieth century would agree to this most modern formulation, which points out the interaction of heredity and environment.

Adams realized the difficulty in recognizing predispositions clinically. "We have rarely any means of discovering it till the disease itself approaches; nor is there any age at which we may call the patient secure [p. 23]." We recognize today that hereditary susceptibilities often are not apparent and may only be uncovered by the most subtle chemical tests.

The treatability of hereditary diseases is generally thought to be a fairly new concept. However, Adams reasoned correctly that those genetical diseases defined by him as predispositions might be prevented or treated by removal or manipulation of the external cause. "When the susceptibility amounts only to a predisposition, requiring the operation of some external cause to produce the disease, there is every reason to hope, that the action of the disease may be for the most part much lessened, if not prevented altogether [p. 27]."

Adams recognized the importance of internal metabolic factors as precipitating causes of hereditary diseases. He singled out puberty, pregnancy, and the menopause as critical periods where a disposition or predisposition might be converted to the overt disease.

A finding frequently encountered in medical genetics is intrafamilial correlation of certain disease features, such as age of onset. Adams recognized this fact, "Hence, those of the children who have passed that early age of onset without any of the symptoms, may be considered as free from the constitutional disposition [p. 21]." Using such information for genetic prognosis, Adams stated, "The danger or security of the rising offspring may often be estimated by a similarity of feature or character to those of their brothers or sisters, who have previously fallen into the disease [p. 22]."

Adams hinted at mutations: "Those constitutions, which are peculiarly susceptible of such diseases as are excited by climate, fall an early sacrifice; hence, the propagation from much sources gradually lessens, and the disease would cease altogether, were it not that parents, free from such susceptibility, occasionally produce an offspring in whom the susceptibility originates [p. 32]." According to modern evolutionary concepts, favorable genetic characters are selected by the environment. Adams wrote: "A race is gradually reared with constitutions best calculated for the climate: a law which, I suspect, has been too much overlooked, in our inquiries after the causes of the more marked varieties in the human species [p. 33]."

He intimated that severe types of hereditary diseases, such as "madness," are often associated with complete sexual apathy and thus may lead to extinction of the trait. He recalled the divine law that forbids mating between close relatives, which would thus prevent increase in hereditary diseases.

Adams was extremely skeptical of man-made negative eugenic measures, such as interference with reproduction, and again finds himself in agreement with most modern human geneticists. "Before we venture to propose measures contrary to one of the strongest impulses of Nature, and to the first blessing which the Almighty Fiat bestowed on man, it becomes us seriously to weigh the consequence [p. 35]." He wisely recognized the difficulties of voluntary celibacy, "It would probably produce its effects only on the most amiable and best disposed, whilst the profligate and unprincipled would indulge themselves, regardless of posterity [p. 35]."

Adams concluded this treatise by requesting the establishment of hereditary registers. Such a plea sounds strangely familiar in the 1950's.

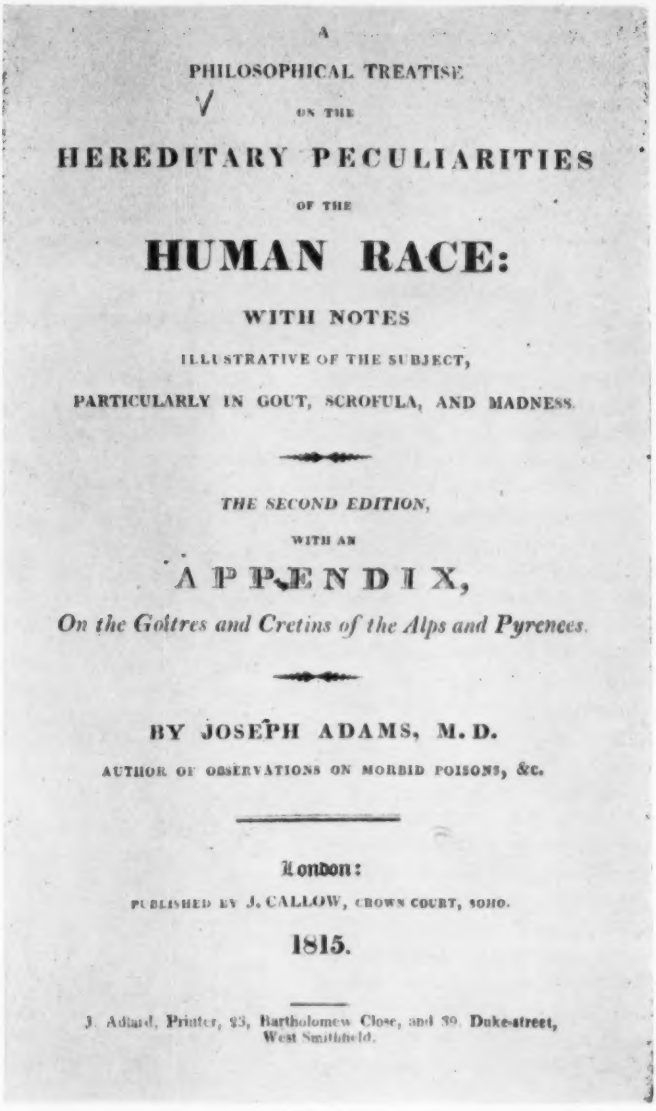
"That to lessen anxiety, as well as from a regard to the moral principle, family peculiarities, instead of being carefully concealed, should be accurately traced and faithfully recorded, with a delicacy suited to the subject, and with a discrimination adapted to the only purpose for which such registers can be useful [p. 41]."

Biographical Data [7,8]

He was born in London in 1756. His father was an apothecary, and young Joseph was made an apprentice in his father's business. In the seventeenth and eighteenth centuries, apothecaries fulfilled the function of the general medical practitioner of today. Originally meant to dispense medicines, apothecaries soon acted as physicians without actually having taken any medical training. Many acrimonious quarrels, and even lawsuits, occurred between the Apothecaries Guild and the College of Physicians. However, near the end of the eighteenth century, it became possible for apothecaries to obtain some medical training.[9] Thus, Joseph Adams attended lectures at Bartholomew's Hospital under Pitcairn, Potts, and Saunders. He later studied at St. George Hospital, where he came under the influence of John Hunter, whose emphasis on evidence, data, and experiments made an everlasting mark on Adams. Adams practiced as an apothecary for some time but did not like this work. In 1795, his first book on morbid poisons appeared.[10] In the opinion of his contemporaries, this contribution was considered his greatest work. In 1796, Adams obtained an M.D. degree *in absentia* from the University of Aberdeen and then went to Madeira, where he practiced medicine for eight years. While on this island, Adams and his wife also ran a sanitarium for invalids from England, charging ten shillings, six pence a day, for "lodging, board, wine, tea and whatever a genteel family expects." In 1801, Adams published a book on cancer of the breast.[11] In 1805, when 49 years old, Adams was elected physician to the smallpox hospital. This appointment was a considerable honor; the laws of the hospital and the statutes of the College of Physicians needed to be waived to allow a member of the apothecaries company to be so appointed. In view of the controversial nature of smallpox vaccination, "the expectation of the whole kingdom was at that time fixed" on reports from this hospital. In 1809, on special recommendation of its president, Sir Lucas Popys, Adams was admitted a licentiate of the Royal College of Physicians without examination. Since it was difficult to be admitted to these examinations, which required considerable classical learning,[9] exemption granted to a man who had not even resided formally at a medical university was a signal honor. Adams published on vaccination, upholding the value of this procedure.[12] In 1809, a small volume dealing with the laws of epidemiology appeared,[13] which again was modern in its concepts. In 1815, the year following the first edition of his book on hereditary diseases, Adams reissued the identical book under a different title, "A Philosophical Treatise on the Hereditary Peculiarities of the Human Race" (Fig. 3).[14] Since Adams expressly stated that his ideas on heredity in man were for the general reader, it is likely that he hoped to attract a wider public with his new title.

Adams was highly esteemed by his contemporaries. For some time he was president of the Medical Society of London, and later he was elected president of the London Philosophical Society. For some years he was editor of the *London Medical and Physical Journal*. Adams died in 1818, at the age of 66 years, presumably from a pulmonary embolus following a fracture of his leg. On his tombstone was the motto *"Vir justus et bonus."* He left no children.

An otherwise laudatory obituary [8] noted that Adams had an "overweening desire for contemporary reputation and an undue irritability to critical animadversion." These traits may be sensed in his book on hereditary diseases. It perhaps is understandable that this ambitious man, with a second-rate apothecary's education, who was not a fellow of the Royal College of Physicians and certainly not of the Royal Society, envied members of these bodies and very much wanted to be one of them. It is also understandable why Adams' contribution to medical genetics was overlooked. Nonmedical scientists interested in heredity were unlikely to pay much attention to a book on hereditary diseases written by an



A

PHILOSOPHICAL TREATISE

ON THE

HEREDITARY PECULIARITIES

OF THE

HUMAN RACE:

WITH NOTES

ILLUSTRATIVE OF THE SUBJECT,

PARTICULARLY IN GOUT, SCROFULA, AND MADNESS.

THE SECOND EDITION,

WITH AN

APPENDIX,

On the Goitres and Cretins of the Alps and Pyrenees.

BY JOSEPH ADAMS, M. D.

AUTHOR OF OBSERVATIONS ON MORBID POISONS, &c.

London:

PUBLISHED BY J. CALLOW, CROWN COURT, SOHO.

1815.

J. Adlard, Printer, 23, Bartholomew Close, and 39, Duke-street, West Smithfield.

Figure 3

apothecary with no real scientific background. The conventionally educated true physicians were too steeped in the classics and philosophy to appreciate the truth of Adams' simple common-sense findings. The most important fact, of course, was the lack of any scientific basis of Adams' observations. Although astute and usually correct, Adams' findings were strictly empiric. Although Adams was usually right in his principles, he often was wrong when giving specific disease examples. Since genetics in the scientific sense was not born until eighty-five years later, it is perhaps not too surprising that Joseph Adams was forgotten. With renewed interest in the ap-

plication of genetics to medicine, however, it seems fitting to honor Joseph Adams as one of the pioneers in the field.

Summary

In 1814, a London apothecary-physician, Joseph Adams, published a book entitled "A Treatise on the Supposed Hereditary Properties of Diseases Based on Clinical Observation." The identical book was reissued in 1815, under the title "A Philosophical Treatise on the Hereditary Peculiarities of the Human Race." The author showed remarkable insight into some principles of human genetics.

The aim of the book was to furnish a guide for heredity counselling. Adams made the following observations. 1. There is a clear distinction between congenital, familial ("recessive"), and hereditary ("dominant") conditions and their patterns of inheritance. 2. Some of the characteristics of familial (recessive) diseases were noted, i. e., mating between relatives would increase the disease frequency. 3. Hereditary diseases may manifest at various age periods and not necessarily at birth. 4. Hereditary susceptibilities exist which need external precipitating factors to make illness apparent. In terms of risk for offspring, it is immaterial whether clinical disease is present or not. 5. Genetic illness may be treatable, especially if precipitating factors may be removed. 6. Intrafamilial correlation of age of onset of hereditary diseases exists and is clinically useful in genetic prognosis. 7. Genetic heterogeneity of clinically identical disease were hinted at. 8. Increased hereditary disease frequency in isolated districts may be caused by inbreeding. 9. Mutations were predicted. Adams' attitude to practical eugenic measures was critical. He concluded by calling for the establishment of hereditary disease registers for further study.

Joseph Adams' career is described, and the failure of medical scientists to note his observations is discussed.

This work was done during a stay at the Galton Laboratory, University College, London, with support of the Commonwealth Fund. Joseph Adams' book was found in the University College Hospital Library. Miss Jesse Dobson, Curator of the Anatomy Museum, Royal College of Surgeons, helped with 19th century sources.

Department of Medicine, University of Washington (5).

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Contributions of Basic Science to Modern Medicine

Immunity, Infection, and Properdin

RALPH J. WEDGWOOD, M.D., Cleveland

The word "immune" derives from the Romans, who used it to describe those persons declared exempt from taxation and other obligations to the state. The meaning was later applied to the exemption and protection due to the early Christian church and its officers, as in "papal immunity" or the "immunity from arrest" found in the sanctuary of the church. The understanding of the word changed from the concept of "exemption" to the connotation "rendered safe," and usage implied that such protection was innate.

"Immune" was thus the word applied to that state in which animals were protected or rendered safe from an infectious agent, either by prior infection or by experience. The substances which appeared in the serum under these circumstances were logically called "immune bodies"; they later became "antibodies," and again, logically, immunity —the state of refractoriness to infection— was equated directly by many persons with such circulating antibodies.* The state of immunity was, in addition, considered as being an almost absolute phenomenon of complete freedom or exemption from the infection.

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Departments of Pediatrics and Preventive Medicine, Western Reserve University School of Medicine.

This work was conducted in part under the auspices of the Commission on Acute Respiratory Diseases of the Armed Forces Epidemiological Board and supported in part by the Office of the Surgeon General, Department of the Army, Washington, D. C.

* Not, however, without the discussions of Erlich and Metchnikov as to the relative importance of antibodies and reticuloendothelial system.

Such conceptual rigidity is, of course, unbiologic. Refractoriness to infection cannot be considered as an all or none occurrence. Infection is the resultant of the interaction of all the various forces of both the infectious particle and the involved host. Each of the multitude of reactions is subject to biologic variability and to random hazards of chance occurrences. Serologic substances are only one group of participating host factors and probably play only a small role in the general phenomenon of resistance to infection. Specific serologic immunity from antibodies would constitute a still smaller portion. The substances in blood, and particularly in serum, have received attention, perhaps because of their ready availability and ease of study rather than their importance.

If "immunity" is to be equated with protection against infection obtained by prior experience and related therefore to antibodies, then certain semantic difficulties can be avoided by referring to protection provided by innate, noninduced host factors as "natural resistance." Such differentiation works well for well-defined systems. However, definition is not needed in well-defined areas. The distinction has not helped to clarify those areas lying between the two extremes, for example "natural immunity" associated with "natural antibodies." † It is in these ill-defined areas that definitions are usually most sought after. They are, at best, a mixed blessing. As the subjects them-

† There is not at present general agreement as to the meaning of the term "natural" or "normal" antibodies. These may be no more than cross reacting antibodies induced in the usual manner by exposure to different but antigenically related antigens.

selves become more clearly understood, similarities and differences become more apparent and definitions less important.

This paper will describe the nature of a serologic factor, properdin, and discuss its possible role in the mechanisms by which a host may be rendered safe from infections. Four topics will be presented as follows:

1. The potential role of serologic factors in the host reaction to infection.
2. The identity of properdin.
3. The identity of the interaction of properdin with various infectious agents.
4. The biologic activity of properdin in vivo.

1. The Potential Role of Serologic Factors in the Host Reaction to Infection

The first requirement for successful infection is penetration of the host integument by the infectious agent. The physical properties of the skin and mucous membranes and the inhibitory substances that they secrete (for example, lysozyme) are effective barriers to penetration. In addition, local bacterial (and perhaps viral) flora with which the host lives in symbiosis resists, by competition for essential nutrients, among other things, the invasion of new exogenous agents. The survival of higher animals in a world which is numerically one enormous microbial hazard is perhaps the best monument to the efficacy of these surface factors.

With the rare exception of those few unusual infections which are introduced directly into the tissues or blood by third-party vectors, all infecting agents must pass this barrier, either by active penetration of their own making or passively, through some defect attributable to the host. This is a local affair, and local factors must be, therefore, of prime importance. Except when eroded surfaces are bathed with exuded serum or flooded with blood, circulating immune factors probably play little part in resisting the act of penetration by the infecting agent.

After penetration, infectious material is rarely disseminated directly into the circulation. What has been termed "primary lodgement," or "nidation," takes place before further invasion occurs. The period during which nidation takes place has been called "the decisive period," and it is at this time (in bacterial infections at least) that the local inflammatory responses,‡ which characterize the infectious process, begin. In the experimental animal, this period is short, a matter of minutes or, at the most, hours. While the local inflammatory lesion may progress for hours or days, it is only during the short "decisive" period that the future development of these local changes can be affected by such things as the physiologic state of the host (for example, shock) and by drugs (such as epinephrine or antibiotics). This is the reason for the term "decisive period." After this time, therapy may sterilize the area, prevent dissemination of the organisms, or eliminate the production of toxins, but the host tissue changes initiated with the inflammatory response continue unaffected. It is presumably during the decisive period that serologic factors may first have an effect in "natural resistance." [1,2]

Following primary lodgement, or nidation, host damage may result from a variety of different progressions. Direct local extension of the lesion may damage some vital structure, and it would presumably be resisted again, primarily by local forces. Alternatively, widespread dissemination may occur through lymphatic or hematogenous seeding. In this case, serologic factors would logically be expected to have their greatest effect, either by actual destruction of the infecting agent or by potentiating the removal and sequestration of the agent by tissues containing phagocytic cells. The result of intracellular sequestration would depend again on local factors, particularly the intracellular environment and the biochemical and physiological ability of the host cell to adapt to the parasite and vice versa. Finally, even without actual exten-

‡ The pathologic progression from increased vascular permeability, stickiness of the vascular endothelium, diapedesis of leukocytes, edema, and induration to thrombosis of blood and lymphatic vessels with subsequent necrosis.

sion of the infectious particle directly to other tissues, host tissue damage may be brought about by endo- or exotoxins and released by the invading organism. These may be neutralized by serologic factors. The classic reaction of toxin and antitoxin is perhaps the best and most easily demonstrable specific example of the protective role of antibody. Toxins may also be neutralized nonspecifically, such as the neutralization of endotoxin by factors present in normal plasma.[3] In addition, on a local level the effects of the toxins may be negated by innate refractoriness of the tissue.

In any instance of infection, experimental or natural, these steps cannot properly be considered or usually isolated as distinct entities. Careful control of experimental conditions has made it very apparent that a remarkable number of defense mechanisms do exist. In any one infection perhaps only a few of these are called into play. But even though only a few may be called into critical participation at any one time, all must be considered in the evaluation of the over-all response,[4] resistance to infection.

2. The Identity of Properdin

It has been known for many years that when zymosan, the insoluble cell-wall residue of yeast, is incubated at 37 C with serum, a portion of complement known as the third component (C'3) is inactivated.§ However, when serum is incubated with zymosan at 15 C, little or no inactivation of the third component of complement occurs. But at this temperature, zymosan is found to combine with a serum protein, properdin, which is necessary for the inactivation of the third component at higher temperatures. This protein can be eluted from zymosan. It was called properdin from the Latin *pro* and *perdere*, meaning to prepare to destroy.[5-8] Properdin, with complement and magnesium, has a variety of biologic activities: the lysis of certain bacteria[9] and erythrocytes,[10,11] the inactivation of some viruses,[12,15] and the destruction of at least one protozoan.[16,17] These activities have logically led to the assumption that it should play some role in natural resistance to infection.

The interaction of properdin with zymosan and its ability to elute from zymosan have made possible a high degree of purification. With use of this principle, preparations purified (on the basis of activity per unit nitrogen) up to 2,500 times with respect to serum in yields of 40%-80% have been obtained. Usually, such preparations contain 900-1,000 units of properdin per milligram of nitrogen. Normal sera contain approximately 4-10 units per milliliter. Thus properdin constitutes less than 0.05% of the serum proteins.[8,18,19] Yet, in spite of 2,500-fold purification, such preparations have been found to be heterogenous chemically, biologically, and immunologically. Further purification is presumably possible, and the figure of 0.05% of serum protein probably represents an overestimate.

Properdin can be removed selectively and completely from serum by careful adsorption with zymosan. The resulting serum, having a residual of less than 1%-5% of the original properdin, seems, in most other respects, unchanged. The components of complement, clotting factors, isoagglutinins and antibodies, and enzymatic activities, such as plasmin, amylase, lipase, phosphatase, and lysozyme, remain.

When properdin is added back to properdin-deficient serum (RP) and the mixture is incubated with zymosan, the third component of complement (C'3) is inactivated. In the absence of properdin this inactivation does not occur. It is by this reaction that properdin is defined and upon this reaction that most assays for properdin are based. The reaction is, however, complex; only the terminal step is usually measured. There are other steps and other serum factors which are required. These, too, can limit the reaction, thus affecting experimental results and the measurement of properdin.

The removal of properdin from serum by zymosan seems to be selective, as shown by

§ Throughout, only data relating to the use of human serum will be discussed.

the high degree of purification afforded by its use. However, zymosan is a particulate substance and will interact with other proteins in serum.‖ Thus, properdin preparations have been found to contain, along with properdin, a variety of other substances having biological activities, including enzymes, such as phosphatase and lysozyme. Some preparations have contained isohemagglutinins and agglutinins for zymosan. The adsorption of such enzymes and agglutinins seems to be nonspecific. These same factors are also found in the properdin-deficient serum (RP) and are not concentrated by the adsorption process. The agglutinin for zymosan has been readily distinguished from properdin by suitable cross adsorption. Indeed, in all cases to date, the biologic activities exhibited by purified properdin preparations alone (in the absence of the other serum factors of the properdin system) have been found to be distinct from the biological activities described for the properdin system itself and thus can properly be considered as being due to contaminating substances.[20]

Immunochemically and physicochemically, properdin preparations are also heterogeneous. Antisera prepared by the injection of such preparations into rabbits indicate that there are at least five immunochemically distinct antigens. Cross adsorption experiments suggest that only one of these is properdin itself; the other four antigens are also present in properdin-deficient serum (RP). Analysis of concentrated purified material by sedimentation behavior and electrophoretic mobility suggests that the active material is a large globulin, corresponding probably to the γ_1-globulins.[20] ¶ Data of Pillemer[21] and Isliker[22] indicate that aggregation and dissociation of the protein may take place; properdin thus may resemble the macroglobulins.

Properdin would seem from these many points of view to constitute a distinct serum protein. However, its distinctive features and its high degree of purification do not preclude biological marco- or micromolecular heterogeneity.

3. The Identity of the Interaction of Properdin with Various Infectious Agents

The properdin system has been shown to be involved in the lysis of certain bacteria and erythrocytes and the inactivation of some animal and bacterial viruses by normal human serum.[9-17] The affected bacteria are, in general, Gram-negative. There is, however, no obvious distinction between those strains of bacteria which are susceptible and those which are resistant other than the lytic activity of the system. The phenomenon of susceptibility seems to be a distinguishing property of the strain (or perhaps of the individual bacterium), not of the species or genera from which the strain is derived.[9] Viruses have not been as closely screened for susceptible and resistant strains. Those animal viruses which are apparently susceptible belong in general to the myxoviruses.[12] Reviews of the literature, however, suggest that other viruses may also be affected in whole or part by the system.[12] At least two distinct bacterial viruses are also inactivated by the properdin system.[13,15]

The term "system" is employed because properdin alone has no effect. Activity requires other serum factors, which resemble the four components of complement. In addition, the reactions require magnesium, are pH- and ionic-strength-dependent, and are markedly affected by temperature. The similarity of requirements in these biological activities constitutes one argument in favor of their being caused by similar, if not identical, substances. The multiple require-

‖ Interaction of particulate substances with serum proteins is a common phenoenon. Other materials, such as $BaSo_4$, starch granules, charcoal, or crushed glass, have similar nonspecific adsorptive properties.

¶ In previous publications, properdin has been termed a β-globulin. This class of proteins has indeed been designated by a variety of terms; β_2-globulins, slow-moving β-globulins, fast-moving γ-globulins, etc. Current usuage, however, seems to favor the term γ_1-globulins.

ment for other factors along with properdin renders the term "system" conceptually useful.

There is discussion as to whether properdin is or is not an "antibody." Much of the controversy is based on definition. Pillemer thought of properdin as a "primordial antibody,"[21] but he also pointed out that there are distinct differences between properdin and usual antibodies. The most distinctive of these differences is the requirement for serum factors in the interaction of properdin with polysaccharides (and as has been demonstrated since, with viruses). There are, perhaps, analogies in reactions such as those seen in paroxysmal cold hemoglobinuria,[23-25] but the requirement is extremely unusual in the general interaction of antibody with antigen. The question of whether properdin is an unusual antibody[26] (with "low avidity" and thus requiring other factors for interaction with antigen) or entirely distinct from antibody is not perhaps as pertinent as whether the multiple biologic activities exhibited by properdin are due to a single substance[27] or to a variety of distinct and different proteins, pooled as an artifact of preparation. Data available at this time suggest that properdin is probably a distinct protein with multiple biologic activities. The evidence supporting this concept is necessarily indirect, and none of it is in any way conclusive.

The removal of properdin from serum with zymosan is reflected by a loss of certain specific bactericidal, erythrolytic, and virus-neutralizing activities. This biologic phenomenon has been well demonstrated for a variety of infectious agents and erythrocytes. The interaction of properdin with zymosan seems specific, as attested by the purification of properdin provided by its use. The selective removal of activity is, in itself, suggestive of identity. The readdition of properdin restores bactericidal and virus-neutralizing activity to the properdin-depleted serum. Only very small concentrations of properdin ($\frac{1}{10}$-$\frac{1}{100}$ of that found in normal serum) are required. Preparations of properdin prepared and concentrated in different manners and concentrations give similar activity under such circumstances, whether assayed by interaction with zymosan or by bactericidal or virus-neutralizing activity.

This correlation has only been demonstrable under the carefully controlled conditions of adding properdin back to properdin-depleted serum (RP). In measuring the activity of random specimens of sera by different methods, this correlation is not found. However, the over-all interaction of serum with virus, bacterium, or erythrocyte, resulting in virus neutralization, bacteriolysis, or erythrolysis, is a multistage reaction requiring several other distinct serum components. Only the terminal phase of the reaction is measured. Many things other than properdin, including factors required for and factors inhibiting activity, may limit the reaction. Thus, the fact that there is no relationship between properdin titers as measured by the zymosan assay and the neutralization of phage[13,14] or the lysis of bacteria[9] and erythrocytes[11] in random sera, or that various sera inactivate different bacteriophages to different degrees,[27] cannot be interpreted directly as indicating that properdin is a heterogeneous group of substances, each with different activities. The effect of the factors other than properdin must also be considered.

Zymosan is not the only material that removes properdin from serum. Many other polysaccharide-containing substances interact with properdin.[28-30] Such substances have been derived from diverse sources, included yeasts, bacteria, and mammalian tissues. The removal of properdin from serum by such substances (as measured by the zymosan assay) also affects bactericidal[29] and virus-neutralizing activity.[30] Thus, the activities ascribed to the properdin system are affected by the same variety of different polysaccharides. It would seem unlikely that each of these polysaccharides had multiple different receptors arranged in such a manner as to remove simultaneously

multiple different substances from serum in a similar manner.

Properdin is antigenic.[31,32] Antisera to properdin cross adsorbed with serum deficient in properdin produce a single distinct line of precipitate when reacted against properdin by agar-diffusion techniques. Such adsorbed antisera inactivate properdin when measured either by interaction with zymosan, by bacteriolysis, by erythrolysis, or by virus neutralization. Quantitatively, the degree of inactivation is, within the limits of the techniques used, similar. Such data certainly suggest that properdin is a single substance antigenically and that the bactericidal, erythrolytic, and virus-neutralizing activity are identified with the same antigenic material.

These findings are then consistent with the hypothesis that the activities ascribed to properdin (interaction with certain polysaccharides, lysis of some erythrocytes and bacteria, and the inactivation of a few viruses) are due to the same substance and that in these activities gross macroheterogeneity does not exist. This does not, however, indicate that micromolecular heterogeneity is not present. It has been stated,[33] "All protein preparations prepared so far represent populations of closely related members of a family, not collections of identical molecules." In the case of properdin, the data suggest a family resemblance but do not prove identity.

4. The Biologic Activity of Properdin in Vivo

Properdin is found in the sera of almost all normal mammals. It apparently has a variety of activities against infectious agents in vitro. It would seem logical that it should have some biologic function in vivo. Such a function has yet to be demonstrated. However, this is not an unusual circumstance; it has been difficult to show a protective role for many other serum factors in the intact animal.

Properdin does appear to be involved in the host response to the injection of bacterial (and other) lipopolysaccharides or endotoxins.[15,34-38] After injection of such lipopolysaccharides, there is usually a distinct variation in the serum properdin titer—an initial fall in level, followed by a rise to values above normal. Concomitant with such changes, there occur variations in susceptibility to challenge infection, in most respects analogous to the negative and positive phases described by Sir Almroth Wright after typhoid immunization.[1] The low properdin levels are generally associated with increased susceptibility, the high levels with increased resistance to infection.# However, the changes in properdin level and in susceptibility to infection are not necessarily related causally. There are, as previously discussed, a great many other host factors involved in "natural resistance." The injection of endotoxins has a variety of effects in addition to those of changing properdin levels. The properdin titer may be an index of a response rather than a causal factor in the response.

Properdin titers in man have been found to vary from the normal range in a variety of diseases.[39-42] There has been acute interest in reports that patients with advanced cancer have low properdin titers. Attempts have been made to relate such properdin titers to resistance to neoplasia and to homotransplantation of tumors.[41,43,44] No distinct relationship has been demonstrable. It seems again possible that the variations in measured properdin levels reported in these diseases are indices of a response to a disease (perhaps tissue breakdown) and may, therefore, have no direct or causal relationship to the illness itself.

The effect of the administration of properdin to experimental animals has also been studied.[32,44-46] Administration of properdin under some selected circumstances has been associated with increased resistance to challenge infection and irradiation. However, the effects have been slight, variable,

This increase in resistance has also been tested with the use of an artificial viral infection (staphylococcal phage in rabbits) with similar findings.[35]

and inconsistent. The positive results cannot be interpreted as showing a unique protective effect from properdin. Experimental animals show a similar increase in resistance to infection following the injection of a variety of nonspecific substances.[47] Boiled properdin, which has no activity in vitro in the properdin system, also gives significant protection in the intact animal.[45] The negative results should not, however, be interpreted as indicating that properdin has no role in vivo. The experimental conditions for such a demonstration may be inadequate at this time.

The experimental approach of giving properdin to animals and subsequently studying their resistance is more complicated than would be expected from initial consideration. The problems of present experiments involve three major considerations. First, as previously pointed out, current properdin preparations, while highly purified, are heterogeneous. The effects seen following injection may well be due to contaminants, not to properdin, which may explain the results with boiled properdin. Until more adequately purified preparations are available, the differentiations between the effect of properdin and the effects due to contaminants will be hard to distinguish. The second consideration is that properdin is an unstable substance, and following experimental intravenous administration the expected rise in serum titer is not always found.[32,44] The administration of properdin cannot, per se, be equated with increased serum properdin levels. Finally, properdin is antigenic, and repeated administration may result in the production of antibodies which can block the anti-infectious activity of the material in vitro and thus presumably in vivo. Such antibodies may cross react with properdin from different species, including the properdin of the host which forms the antibodies.[13,14,31,32]

Thus, while data are available indicating increased natural resistance following the administration of properdin or substances which increase properdin levels, evaluation of the data does not allow the interpretation that properdin has any influence in itself. It is equally true that data reporting a lack of correlation cannot be construed as indicating that properdin has no role in such matters. As pointed out in the initial section of this paper, natural resistance involves a multitude of factors. Under ideal experimental conditions it may be possible to demonstrate their role, but it may not be possible with current methodology to control the many other factors in such a way as to allow visualization of the effect (if any) of properdin.

These problems of proving causation or effect are not unique to properdin and complement. They are encountered in many types of experimental procedure involving intact animals. Another, perhaps more generally recognized, example is the effect of steroids on infection, about which a great deal of data has been collected, yet with little actual resultant over-all increase in understanding. It is very possible that only through the development of new approaches or by the finding of natural experiments (such as agammaglobulinemia has proved to be in understanding of the role of antibodies) will the role of properdin ever be satisfactorily elucidated. Until such time, interpretation of concomitant findings requires considerable caution. The fact that properdin exists in serum, has many biologic activities in vitro, and, in at least a temporal manner, is related to change in resistance in vivo makes it probable that there is some biologic role and that this should be demonstrable in the future by proper techniques.*

Summary

An attempt is made to discuss the relationship of properdin to immunity and natural resistance to disease. It is pointed out that the host response to infection involves a great many factors, only a few of which are in serum, and that properdin is only one of these many potential protective serologic substances. The nature of proper-

* This article is not intended to be an exhaustive review. Other reviews have recently appeared.[40,49]

din, some of its properties, and its interaction with infectious agents in vitro are described. The opinion is presented that properdin is a distinct protein and that the biologic activities attributed to properdin in vitro are due to this protein. Reasons for this opinion are given. It is pointed out that the data are not conclusive and that other valid interpretations can be made. The possible biologic role of properdin in vivo is commented upon. It is suggested that while properdin probably has some biologic role in vivo, this role has yet to be proved adequately.

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Books

EDITED BY WILLIAM B. BEAN, M.D.*

Science, Theory and Man. By Erwin C. Schrodinger, Nobel Laureate. Price, $1.35. Pp. 223, with many illustrations. Dover Publications, Inc., 920 Broadway, New York 10, 1957.

> Now, whether these effluviums do fly by striated atoms and winding particles, as Renatus des Cartes conceiveth, or glide by streams attracted from either pole and hemisphere of the earth unto the equator, as Sir Kenelm Digby excellently declareth, they take not away this virtue of the earth; but more distinctly sets down the gests and progress thereof, and are conceits of eminent use to salve magnetical phenomena.
>
> SIR THOMAS BROWNE, PSEUDODOXIA EPIDEMICA.

It must be thoroughly exasperating for a brilliant mathematician and physicist to try to present to laymen a summary of his work and speculation. This is especially true when one is dealing with the mysterious conflicts between quantum and wave mechanics, which have plagued experts in the field. When Schrodinger was professor of mathematical physics at Zurich, he established his theory of wave mechanics, setting forth what is now known as the Schrodinger wave equation, the basis of modern quantum mechanics. It has been his thesis that the aim of physics is to discover the fewest possible simple and fundamental laws which will comprehend each separate phenomenon in the great mass of the complex phenomena of existence. When classical physics did this and extended its mechanical method to all parts of physics, it tried to explain all natural processes by making models. Now that relativity and quantum mechanics have overreached "simple" Newtonian physics, one burning question which persists concerns the usefulness of the general principle of causality. The notion of strict causality has been draining away in contemporary science. Heisenberg's uncertainty principle has given rise to certain logical consequences in Schrodinger's conceptual patterns. It is fitting that persons dealing with uncertainty principles have not solved these vexing puzzles.

In submicroscopic physics the nature of matter keeps us from knowing the location and velocity of a particle at one and the same instant. This prevents us from predicting the subsequent state and place of the particle. In theory interference induced by the very act of measuring alters the position of the electron itself, and so causality comes a cropper. Reality is approached now through mathematics. This entaiis using statistics as a means of dealing with probability. Statistics to handle huge totalities becomes a part of the new methodology of modern science.

Schrodinger says, "Cartography and registration are used by all of us for the purpose of securing the correct orientation quickly in regard to each single case as it turns up; but the essential feature of statistics is the *prudent and systematic ignoring of details.* This is a typical instance wherein a new trend of interest entails the shifting of all questions and gives rise to entirely new ones. . . . To establish the necessary order and lawfulness in the human community, with the least possible interference in the private affairs of the individual, seems to me to be the aim of a highly developing culture. For this purpose the statistical method as used by the physicist appears very appropriate. In the study of the human community it would mean the study of the average mind and the average human gifts, taking into account their range of variation, and from this to infer what the motives are that must be put before human beings to appeal to their desires so as to secure a social order that is at least *bearable* in all its essential features." Thus we have to move from physical models to mathematical formulae. Modern physicists have come close to dealing with the universe as a world of pure thought, a grand mathematical abstraction.

After I had finished reading over this book on "Science, Theory and Man," I had the illusion for a short time that I understood the major aspects of the thesis. At other times I have thought that I had a reasonable grasp on current concepts of the coagulation process

* Communications to this Department may be sent directly to Dr. William B. Bean, University Hospitals, State University of Iowa College of Medicine, Iowa City, or to the Chief Editor for transmittal to him.

just after the speaker had finished talking or I have closed the pages of the book. Soon a certain species of indeterminism has prevailed I could no longer reproduce in my own mind that which recently seemed so clear.

It should surprise no one that the temper of the times or the climate of opinion influence and are influenced by science. It is Schrodinger's view that the erosion of simplicity and purposefulness in the arts and crafts has altered the whole character of painting and craftsmanship. The change which has taken us from Da Vinci and Michelangelo to Picasso and Dali parallels the change which has taken us from Newton to the modern physicists of the atomic age. We are beginning to make our picture of the physical universe as far as possible out of verified facts and not ornamental accessories, and if there is much bare space in the nearly empty room of an atom we have also the bareness of modern interiors and the employment and even enjoyment of a room which is almost empty rather than filled with Victorian clutter. At the same time with these changes has come with a great deal of unrest, not just that of the beatnik, but a profound skepticism with regard to all principles which have been accepted traditionally. While this is to some extent a characteristic of all ages, the desire to evade being carried on the current of tradition affects every branch of human activity and all classes of people. Whether we like it or not we should at least face it as a fact. Thus, in making the great change from a fixed and stable view of religion to the shifting sands of evolution and from the comfort of invariance to the instability of relativity, in science we are going through the same thing which pervades our whole culture. Whether this is a prelude to holocaust or jostling before settling down in a better approach to the good society remains to be seen. A thoughtful man, however, finds very little comfort in realizing that these trends are imbedded in and activate great swarms of people.

Unhappily, man in masses tends to follow the lowest common denominator and exemplify colossal and all-pervasive ignorance. This, too, should not be disconcerting when we realize how recently and how little we have departed from Neanderthal man. Now we return to the ancient posture of the Sophists, whose exciting claim was that by the art and craft of words they were able to establish the truth of either one or the other of two contradictory and mutually excluding statements. Implicit now in our word "sophistry" is the notion that skulduggery has been committed and we have been duped. Perhaps, though, a deeper meaning which Sophists may have had was in recognizing the great intermediate gray zone which separates the more or less hypothetical extremes of right and wrong, or black and white, or true and false. Though in science we try to pose a question so that the answer is yes, no, or how much, data from our most assiduous efforts may do little more than tell us that *it depends*. Schrodinger believes that the real crux is to manage *it depends* in such a way that the contradictions which lead to the dilemma cancel out.

The main point for clinical scientists and physicians to learn and to remember is that we need to keep a very sharp eye on intellectual "body English," lest conscious or unconscious contortions confuse us into thinking what we want to rather than what the evidence tells us. There are passages in this book that give one the interesting feeling that the influence of Bishop Berkeley is permeating physics once more. The insubstantiality of atomic physics, even with language barriers trimmed down to a minimum, may go a long way toward explaining the constructs of the mathematical geniuses who are making advances in this field, but for the physician the shadow of Bishop Berkeley and his contributions to unreality should not let us forget his medical heresies and advocacy of Tar water as a universal panacea on the basis of what we know now was totally inadequate evidence. Perhaps my understanding of Schrodinger's book is equally faulty, but it is full of stimulating ideas and wise in its fearless approach to a clearer philosophy.

WILLIAM B. BEAN, M.D.

Clinical Epidemiology. By John R. Paul, M.D. Edited by Peter P. H. De Bruyn, M.D. Price, $5. Pp. 291, with 37 illustrations. The University of Chicago Press, 58th St. and Ellis Ave., Chicago 37, 1958.

Epidemiology is not a pure science but a collective one, utilizing information from many disciplines to understand better the natural history of disease, whether infectious or non-infectious, as it relates to the environment, the host, and the parasite, or, as J. E. Gordon puts it, "the world, the flesh and the devil." The author of "Clinical Epidemiology" is well acquainted with all the facets of the subject and has for a long time carried on important

studies in the field, using the laboratory as his handmaiden. Dr. Paul is also a teacher of preventive medicine and, like many of his confreres in his endeavor, has faced the problem of attempting to make epidemiology come alive, so to speak, to medical students. He has drawn illustrations of the epidemiological approach by emphasizing the clinical aspects of the subject and stressing the surroundings of the family and the factors that influence illness within the family setting. This method is well documented. However, the subject matter of the volume is not confined to this approach.

Epidemiology has outgrown its former limits of attention solely to infectious diseases to encompass noninfectious conditions, like heart disease, cancer, and diabetes. Application of the method to noninfectious disease is adequately covered in the section on "Sample Diseases."

The book begins with a short introduction which sets forth the author's philosophy with relation to clinical epidemiology. The remainder is divided into three parts, namely, a first part, of three chapters on "Definitions and Concepts, Old and New"; a second part, of twelve chapters on "Principles," and a third part, on "Sample Diseases." This is followed by an appendix, which treats of "Medical Certification of Cause of Death and Guides for Planning Serological Surveys." An adequate bibliography and a short combined author and topic index complete the book, which throughout is additionally well illustrated with thirty-seven portraits, figures, and tables, which add considerably to the factual material.

The volume is straightforward in its approach at a scientific level and easily read because of the large type and excellent paper used. The book is recommended to all those whose work is even remotely connected with epidemiological methodology and application, including all medical and ancillary disciplines whose members conduct studies utilizing epidemiological methods. Oddly enough, many persons unwittingly use them in studies they are conducting.

FRANKLIN H. TOP, M.D.

A Symposium on the Evaluation of Drug Toxicity. Edited by A. L. Walpole, Ph.D., B.Sc., and A. Spinks, M.A., Ph.D., B.Sc. Price, $5.50. Pp. 138, indexed. Little, Brown & Company, 34 Beacon St., Boston 6, 1958.

This is a refreshing book. The formal presentations are for the most part unhackneyed, and the discussions are lively and thoughtful. I found the chapter by Hurst on sexual differences in toxicity of drugs and the one by Paget on the morphological evaluation of toxic action particularly stimulating. (Paget's "routine" histopathology looks fantastically complete, by comparison with American standards!) John Litchfield, the only American at the meeting, supplies another high spot with his thoughtful, off-beat analysis of "screening" for efficacy and toxicity.

The volume is also pleasantly brief and can be held comfortably in one hand while one is lying in bed. It is recommended to pharmacologists and to those clinicians concerned with the investigation of new drugs.

L. LASAGNA

The Differential Diagnosis of Abdominal Pain. Edited by Sherman M. Mellinkoff, M.D. Price, $9. Pp. 443, with 29 illustrations. The Blakiston Company (division of McGraw-Hill Book Company, Inc.), 330 W. 42d St., New York 36, 1959.

A neat balance is achieved in this short volume between information useful to the surgeon and that primarily of value to the internist. The result, a handbook filled with numerous facts about a diversity of diseases and conditions, should help to serve as a chart to guide physicians between "Scylla and Charybdis, between the dangers of operating too much and too little."

Basic physiologic and neurologic considerations are briefly and comprehensively treated by Thomas Almy, Professor of Medicine at Cornell University Medical College. His contribution comes closest in this volume to fulfilling the object of the handbook, to present recent useful research contributions and other up-to-date information not otherwise available in published books. Had the other section authors followed his precept closer, this volume would be an outstanding contribution to the literature of diagnosis.

Victor Richards, Professor of Surgery, Stanford University School of Medicine, makes the longest contribution to this work. His section on history, physical examination, and the definition of terms used in describing physical findings is excellent and lucid. The remainder of this portion is repetitive, contains generalizations, and lacks statistical information which would be of great utility. Perhaps the panel type presentation, which is the source of the book, is the cause of these deficiencies.

A compact presentation of the retroperitoneal causes of abdominal pain deserves compliment, and the numerous, well-chosen case presentations emphasize these conditions in a dramatic fashion.

The editor of the volume proves to be a talented writer who brings clarity, metaphor, and humor into his contribution on the systemic diseases that cause abdominal pain. His section is comprehensive without being heavy, brief without being incomplete, and has a light touch which is not frivolous.

Although the volume is somewhat repetitious and would profit by more illustrations and statistical tabulations, it will be useful to physician and surgeon alike and will be of value as a source of review information. The individual chapter bibliographies contain well-chosen, recent articles of importance.

JOHN J. BERGAN, M.D.

Instrumentation in Anesthesiology. By William H. L. Dornette, M.D. Price, $8. Pp. 242, with 130 illustrations. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1959.

Recent developments and continuing expansion to the area of monitoring various phenomena which occur during the anesthetization of patients undergoing surgery make it highly desirable that those administering anesthesia be familiar with the monitoring methods. Thus, the need for a book such as this is real and urgent. The book covers a wide field of monitoring devices and is not limited to those which are electronic in operation but includes a discussion of stethoscopes, blood-pressure cuffs, thermometers, and the methods of gas analysis. At all times the discussion is oriented toward those who have a minimum of background in physics and electronics and, as such, should be readable to all who are practicing anesthesiology. The book begins with a simple review of basic physics and electronics. The presentation is intended to be quite elementary and is perhaps a bit over simplified in some respects. For example, the attempt to explain transistors in two short paragraphs may leave many confused. The area of necessary precautions regarding explosive hazards and asepsis is covered in a separate chapter. A brief discussion of the interpretation and evaluation of results from some of the monitoring devices is included. The book is thoroughly and well illustrated and contains a thorough bibliography. It appears unusual to me that there is definite emphasis on brand names, with the exclusion of certain brands that the authors decide not to discuss. The title of the book may be somewhat misleading in that the contents would be of value to all of those who are interested in the measuring of many physiological phenomena occurring during acute episodes in the practice of medicine. Its value is thus not limited to those in anesthesiology. To those who have a previous background in electronics and physics, this book is probably an over-simplification, but is not written with them in mind. This book probably would fulfill a valuable role in the training programs of residents in anesthesiology and perhaps closely related fields of medicine and would appear to be of value to the practitioner who has a need for monitoring devices and does not have sufficient background to evaluate or use them properly.

WILLIAM K. HAMILTON, M.D.

Cancer: Diagnosis and Treatment. Edited by John B. Field, M.D., with 28 contributors. Price, $18.50. Pp. 812, with 271 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1959.

This text, edited by John B. Field, M.D., was written by a group of twenty-eight physicians, all well versed in the areas wherein they wrote. The neoplastic entities are grouped logically for presentation in a manner which will be familiar to most readers. Four separate chapters are devoted to radiotherapy, chemotherapy, diagnosis, and medical care, and, additionally, there is a chapter on cancer in children.

The material is extremely well presented in an authoritative manner and is easy to read. The format of the book is good; the printing, clear, and the illustrations, ample and well selected. In criticism, there are errors in the bibliography and reference omissions after citation in the written text. It is disappointing that one chapter lists as references sixteen other textbooks.

Among the reasons for the book, as expressed in the editor's preface, is a statement: ". . . no text available to satisfy the student's need for a balanced treatise on all facets of the clinical problems in cancer." This statement and the reference to oncology as an "independent medical practice" may cause wonder and perhaps raise pedagogic eyebrows.

A favorable review is in order. The book is recommended in two areas, particularly, for the hospital library and for the teacher, to whom the chapters will be an aid in outlining a logical clinic or teaching assignment. Others, as the busy student and practitioner, will enjoy the book as a composite review and as a shelf companion for other books.

ROBERT C. HICKEY, M.D.

Eisenstoffwechsel: Beiträge zur Forschung und Klinik. Edited by W. Keiderling. Price, $11.40. Pp. 294, with 138 charts and illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N, 1959.

This is a "Festschrift" written by thirty international authorities on the occasion of Prof. Dr. Ludwig Heilmeyer's sixtieth birthday. It is a beautiful book—well conceived, well executed, and well presented. All aspects of iron metabolism are covered in careful detail, and the information relative to this field is brought up to date. Each paper, in addition to presenting an excellent review of its subject matter, contains an extensive bibliography. This is an excellent source book for all those interested in iron metabolism, whether from the laboratory or the clinical viewpoint.

It is unfortunate that the book is trilingual, some of the papers being in German, others in English, and still others in French.

STEVEN O. SCHWARTZ, M.D.

Praktische Hämatologie: Differentialdiagnose, Therapie, Methodik. By Prof. Dr. H. Begemann and Dr. H. G. Harwerth. Price, $7.10. Pp. 264, with 25 illustrations, 2 color plates, and 17 tables. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N, 1959.

This is a concise, simple paper-bound "handbook" which covers the subject of practical hematology very well. The section on "Diagnosis and Differential Diagnosis" takes up white cell changes, red cell changes, polycythemias, lymph node enlargements, splenomegalies, hemorrhagic diatheses, abnormalities of red cell sedimentation, and the various dysproteinemias.

Treatment is handled separately—in part discussing the various therapies used in hematology in general and in part specific therapeutic agents for distinct entities. Although this approach has some merit, it does make for some discontinuity in reference to specific diseases.

The last section is on methods, both routine and special. These are very well handled, but several are thought somewhat superfluous for a book of this type.

The tables and charts are good, though somewhat complex at times, and contain detail which is not entirely necessary for a handbook. The color plates are highly artificial. The index is very comprehensive.

In summary, a good handbook for student or practitioner, both of whom can gain much useful information from it.

STEVEN O. SCHWARTZ, M.D.

Maternity: A Guide to Prospective Motherhood. By Frederick W. Goodrick Jr., M.D. Price, $1.75. Pp. 130, with 15 illustrations. Prentice-Hall, Inc., Publishers, 70 5th Ave., New York 11, 1959.

This book provides authoritative information on all phases of pregnancy, starting with the first missed period, including the prenatal period, labor, delivery, and the postpartum period. It answers simply but soundly the many questions which concern the average patient. This book will provide the answers to their many problems and allay their many fears. It will also save the physician valuable time so that he can devote his time to more important discussions. In addition, this book provides valuable information concerning the development of the baby and attitudes concerning breast feeding and bottle feeding. There is an interesting chapter for husbands. The author dispels many common superstitions concerning childbearing which are of real concern to many patients.

This book is written in a simple interesting manner, which will make for easy reading and understanding. The physician will find this an excellent book to recommend to his obstetric patients. This will supplement his own recommendations and will emphasize his instructions. It will also serve as a valuable supplement to prenatal class instruction.

This book can be heartily recommended as an excellent authoritative guide for the prospective mother and father.

W. C. KEETTEL, M.D.

Birth of Normal Babies. By Lyon P. Strean, Ph.D., D.D.S., F.A.P.H.A., F.A.A.S. Price, $3.95. Pp. 194, with no illustrations. Twayne Publishers, Inc., 31 Union Square West, New York 3, 1958.

In this book the author attempts to prove that the majority of congenital defects and defective babies can be attributed to the occurrence of stress in one form or the other occurring during the first three months of pregnancy. He offers sixty illustrations of various forms of emotional stress that have allegedly resulted in congenital abnormalities. The author gives examples of excessive pressure on the stomach producing a cleft palate, psoriasis producing a cleft palate, and penicillin rash producing a moron.

There are ten things that the author emphasizes that either should be avoided in pregnancy or should be done. These are as follows: Stress should be avoided. No surgical procedures should be performed during pregnancy except emergency surgery. All x-rays and general anesthesia should be avoided. Potent drugs should be avoided, as well as high-altitude flying. If the patient is exposed to any communicable diseases, γ-globulin should be administered. Multivitamins should be given, particularly B_{12} and B_6, to avoid defects.

This book should never have been published and should not be recommended for anyone to read. There are no scientific proof or any controlled studies presented in this book to substantiate any of the claims. This book, if widely read, will disseminate very harmful information to the lay public. In addition, parents who have had the unfortunate experience of an obstetric death or congenital defects will be made exceedingly unhappy, thinking little things that the wife might have done during pregnancy were responsible for these diseases.

This is the most unscientific publication that I have read, and certainly it cannot be recommended for reading either to the medical profession or to the lay public.

W. C. Keettel, M.D.

Die Gefässarchitektur der Niere: Untersuchungen an der Hundeniere (Heft 5, Zwanglose Abhandlungen aus dem Gebiet der normalen und pathologischen Anatomie). By Prof. Dr. A. Von Kugelgen, Dr. B. Kuhlo, Dr. W. Kuhlo, and Dr. K-J. Otto. Price, $11.20. Pp. 112, with 89 illustrations. George Thieme Verlag, Herdweg 63, (14a) Stuttgart N, 1959.

This volume is the most recent of a series of informal treatises on normal and pathologic anatomy. It deals in considerable detail with the renal arterial and venous systems of the dog, as demonstrated by the injection of "Plastoid," a technique which the authors admit leads to at least forty per cent shrinkage. The photographic reproduction is excellent. There are many schematic diagrams, the most useful of which deal with the interrelationships between the major renal vessels and the major and minor calyceal systems.

The subject is introduced with a discussion of recent trends in renal function by the physiologist, Grupp, whose ruminations take the form of a series of questions. These questions concern renal autoregulation, renal autonomy, low renal venous pressure, and intrarenal heat exchange mechanisms. The reported anatomical studies are designed to supply some of the answers to the physiologist's questions. In most cases, they fail to do so. The book is divided into three papers ("The Arterial System," "The Venous System," and "The Relative Positions of the Arterial and Venous Systems"). They confirm for the canine kidney some of the findings of Trueta in rabbit and man. In addition, they convincingly demonstrate valves in the large renal veins and the sinusoidal nature of many of the largest venous channels, especially in the subcapsular and corticomedullary junction areas.

If one were to take the author's pictures and diagrams at face value it would be necessary to believe that the renal medulla is essentially an avascular structure. This, to my mind, is a major shortcoming in view of recent reports underscoring the magnitude of the vascular compartment in the renal medulla and its importance in postulated mechanisms for concentration of the urine. Unfortunately, neither the anatomist nor the physiologist writing here feels that the monumental studies of Wirz are worthy of even passing reference.

The book is recommended for those who admire painstaking and time-consuming work, well presented, and for those whose interest centers on the renal cortical circulation of the dog. Methodological shortcomings, always a problem, are in this instance an obstacle to total credibility.

C. Larkin Flanagan, M.D.

Patients, Physicians and Illness: Sourcebook in Behavioral Science and Medicine. Edited by E. Gartly Jaco. Price, $7.50. Pp. 600, with no illustrations. The Free Press, 119 W. Lake Street, Chicago 1, 1958.

It would be absurd to blame patients for dying, yet we blame students for failing. Why do they fail? Examine the question for a few unprejudiced moments. I suppose that if one can slough prejudice, one should accept the premise that most medical students are keen, hard working, and not unintelligent. If not, we should change our selection committees. If the premise is valid, we should examine medical education ruthlessly. Simply to disparage failure is facile, superficial and—in education—perhaps defensive, for, as Colton wrote, "Examinations are formidable even to the best prepared, for the greatest fool may ask more than the wisest man can answer." Some students—and physicians—who fail are dull or idle. How many? Were they dull when they gained admission to medical school? If not, why have they changed? We dismiss our failures and punish our criminals, processes which are both practical and reassuring to us all. But let us stop blaming them.

One thing is certain: We sometimes sit around complacently and then belittle others who get on with the job. This has happened with psychiatry and is happening with sociology. For the sociologists are doing what Malleson has called "operational research" into the process of medical education. They may be doing a rotten job, but they are trying. Are we? "Patients, Physicians and Illness" comprises fifty-five articles. Sociologists, cultural anthropologists, and social psychologists have written most of the chapters; physicians have contributed about a fifth. The editor has brought together studies of how behavior and culture influence medical education, physicians, nursing, and the care of the patient. I believe that the editor has tried to do a job worth doing and that he has done it well. I recommend this book to those interested in sociology in medicine. Some faults could be corrected in another edition. The title might be confused with "The Doctor, His Patient, and the Illness," by Balint. There is no index. The articles vary in both substance and exposition; some of them are nothing more than speculations about the intangible by the unintelligible. The title "Basic Functional Roles in Nursing, Mother Surrogate and Healer" recalls Mr. Jorrocks' remark in "Handley Cross": "Hellish Dark, and Smells of Cheese." Contrast it with Lois Hoffman's delightful "How Do Good Doctors Get That Way?" Some sociologists seem to think that turbid writers are the most profound; they should remember the news report which is a model of brevity and clarity: "Bill Smith struck a match to see if there was any gas left in the tank. There was. Aged 47." This is a fascinating book, but is an excellent argument against the introduction of sociology into the medical curriculum.

DANIEL B. STONE, M.D.

Intra Vascular Catheterization. Edited by Henry A. Zimmermann, M.D. Price, $16.75. Pp. 782, with 324 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1959.

So much detailed information has been published on the general subject of intravascular catheterization in the past decade that it would be very difficult for any one person to write a comprehensive survey of developments in the field. Dr. Zimmermann has rendered a notable service in bringing together some of the authorities who have made significant contributions and who have brought new ideas to bear on the problems of cardiovascular disease. The result is a rather detailed compilation of most of the major advances in investigative approaches and their application to clinical problems. This book contains a wealth of information on both the theoretical and the practical aspects of hemodynamic studies. This book is not likely to be outdated and obsolete in a few years because of the fundamental importance of much of the material which it contains.

The chapters of this book have been integrated into a well-balanced treatise. It is well organized. The chapters generally are written in a clear and lucid style. The paper, printing, and format of the book are high in quality, which further contributes to its readability. The illustrations are excellent.

This book will be valuable to anyone interested in cardiovascular problems. It should be particularly useful for the student or physician who is interested in obtaining some basic information on the various techniques and their application.

E. O. THEILEN

News and Comment

ANNOUNCEMENTS

Conference on Diseases of Animals Transmissible to Man.—This year the second annual Midwestern Interprofessional Conference on Diseases of Animals Transmissible to Man is jointly sponsored by the College of Medicine, the State University of Iowa, and the Iowa State Department of Health at Iowa City, Sept. 10 and 11. The subjects covered include brucellosis, rabies, leptospirosis, Q fever, staphylococcal diseases, and others. Presentations are scheduled by veterinarians and physicians and will emphasize the public health practical aspects, and recent advances in these fields.

This conference will be held on a continuing annual basis sponsored in rotation by the academic institutes of the several midwestern states. We would be happy to provide you with any other details required.

Those interested may contact R. A. Tjalma, D.V.M., or Ian Maclean Smith, M.D., Co-Chairmen of the 1959 Conference, State University of Iowa, Iowa City, Iowa.

Special Fellowship in Medical Neoplasia.—Memorial Center is a training center affiliated with Cornell University Medical College. Specializing in cancer and allied diseases, it participates actively in teaching at both undergraduate and graduate levels. It has a fully approved residency program in internal medicine and, in addition, offers special fellowships for study to a limited number of graduate physicians.

I. Scope and Purposes:
   A. To offer the physicians trained in internal medicine the opportunities available at Memorial Center to study the natural history, diagnosis, complications, pathogenesis and pathologic physiology, pathology, and treatment of cancer, with particular emphasis on the leukemias, lymphomas, and allied diseases.
   B. To undertake an active supervised clinical investigation of interest to the service and the fellow in the field of medical neoplasia (nonsurgical cancer and palliative therapy of patients with malignant tumors).

II. Outline of Activities of the Fellow:
   A. The clinical or clinical and laboratory study of an approved or assigned problem under reasonable guidance and supervision. The study is to be carried out at Memorial Center and under the aegis of the Lymphoma Service of the Department of Medicine.
   Available for clinical investigation are hospital records of 40 years, plus an active service consisting of approximately 40 beds in the Memorial Center and two outpatient clinics in which an average of 75 patients are seen weekly.
   B. Attendance at a weekly service teaching conference and medical grand rounds.
   C. Periods of assignment to various surgical clinics and conferences, cancer chemotherapy, radiochemistry, radiophysics, and radiotherapy.
   D. The integrated study of hematology and pathology of cancer.
   E. Observation of the role of the medical consultant to patients undergoing radical surgery for cancer.
   F. An unique opportunity to see and study the management of large numbers of patients with lymphomas, leukemias, and allied diseases.

III. Prerequisites for Appointment to Fellowship:
   A. Candidates must be graduates of recognized A. M. A.-approved medical schools and must have completed or be in process of completing two years of postgraduate training in internal medicine in addition to one year of internship. Such training may be formal residency or its equivalent.
   B. Candidates must be of the highest integrity and moral character and have an expressed interest, both academic and clinical, in the study of malignant neoplastic diseases.

IV. Financial Support:
   A. The salary stipend is $6,000 per annum without maintenance.
   B. The fellowship appointment is for one year, normally beginning July 1, renewable for one or two years for select persons who develop a special interest in some problem.

Applicants should apply in writing to Henry D. Diamond, M.D., Chief, Lymphoma Service, Department of Medicine, Memorial Center for Cancer and Allied Diseases, 444 E. 68th St., New York 21.

First International Congress of Endocrinology.—The program of this meeting, which will be held in Copenhagen, from July 18 through 23, 1960, will consist of 10 symposia and a round-table discussion and of groups of shorter (10-minute) communicated papers. Speakers at the symposia and the round-table discussion are invited by the Congress. Communicated papers may be submitted by investigators in the field of endocrinology, and titles and abstracts are invited. Forms for registration in the Congress, along with forms for the submission of abstracts of short communications, may be obtained by writing to the Congress Secretariat: Dr. Svend G. Johnsen, Hormone Department, Statens Seruminstitut, Copenhagen S, Denmark. The final date for the submission of such abstracts is Dec. 31, 1959. The official languages of the Congress are English, French, German, and Spanish. A volume containing advance abstracts of symposium contributions and the short communications (in one of the official languages and translated into Interlingua) will be distributed to members on registration at the Technical University of Denmark, in Copenhagen. Titles and abstracts of communicated papers should not be sent to the Program Committee, but the Program Committee will review and arrange for the presentation of such papers in appropriate Congress sessions.

Symposium on Fundamental Cancer Research.—The 14th Annual Symposium on Fundamental Cancer Research, "Cell Physiology of Neoplasia," will be held Feb. 25, 26, 27, 1960, at The University of Texas M. D. Anderson Hospital and Tumor Institute.

Van Meter Prize Award for 1960.—The American Goiter Association again offers the Van Meter Prize Award of $300 to the essayist submitting the best manuscript of original and unpublished work concerning "Goiter—Especially Its Basic Cause." The studies so submitted may relate to any aspect of the thyroid gland in all of its functions in health and disease. The Award will be made at the Fourth International Goiter Conference in London, England, July 5-9, 1960, where a place on the program will be reserved for the winning essayist if he can attend the meeting. For 1960, the recipient of the Award will receive consideration for an award of a travel honorarium.

The competing essays may cover either clinical or research investigations, should not exceed 3,000 words in length, and must be presented in English. Duplicate typewritten copies, double spaced, should be sent to the Secretary, Dr. John C. McClintock, 149½ Washington Ave., Albany 10, N. Y., not later than Jan. 1, 1960. The committee who will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

Submission of Abstracts for Fourth International Goiter Conference.—The Fourth International Goiter Conference will be held at the Royal College of Surgeons, London, England, July 5-9, 1960. Abstracts of American papers to be considered for presentation should be sent to J. E. Rall, M.D., National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda 14, Md. Abstracts from all other countries are to be sent to Dr. Selwyn Taylor, 3 Roedean Crescent, Roehampton, London, S.W. 3, England.

All American abstracts must be received by Dr. Rall by Dec. 1, 1959. They should not exceed 400 words and should be submitted in quintuplicate.

Presentation of papers will be limited to 15 minutes, and a copy of the final paper must be sent to the London Secretary two weeks prior to the meeting.

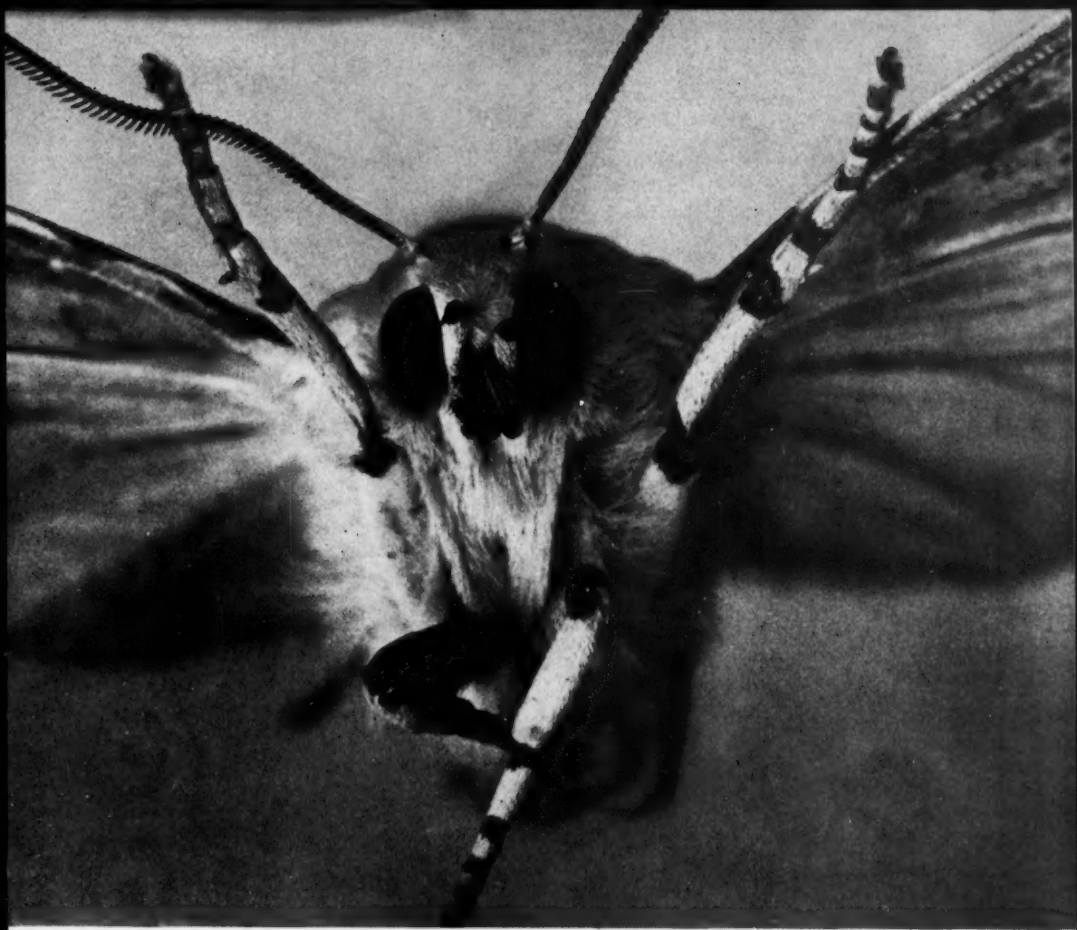
SOCIETY NEWS

International Society of Cybernetic Medicine.—The International Society of Cybernetic Medicine was recently founded with the purpose of assembling researchers engaged in the study of cybernetics applied to medicine and biology and diffusing the methods of research based upon the analogic calculus and the use of electronic models.

Physicians, biologists, engineers, physicists, and mathematicians may become members of this Society.

Applications are to be addressed to the Secretariat-General, presently located in Naples, Italy, 348 Via Roma.

The Society by-laws will be sent on request.



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Although depression has been notoriously resistant to therapy, successful treatment is now possible with NIAMID, a new broad-range antidepressant.

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Animal studies

Animal studies have demonstrated the low toxicity of NIAMID. Hepatic toxicity which has been characteristic of other antidepressant compounds has not been observed with NIAMID in either acute or chronic studies. These toxicity experiments have been conducted in rats, dogs, and monkeys.

Clinical studies

NIAMID, in clinical use, has been characterized by a significant lack of toxicity. It is generally well tolerated. The hepatic toxicity and visual disturbances reported with other antidepressant compounds have not been seen in clinical studies with NIAMID. Orthostatic hypotension has rarely been noted with NIAMID.

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Precautions

Side effects are most often minor and mild manifestations of central nervous system stimulation, modifiable by reduction in dosage. Restlessness, insomnia, headache, weakness, vertigo, dry mouth, and perspiration may be occasional complaints. Care should be taken when NIAMID is used with chlorothiazide compounds, since hypotensive effects have been noted in some patients receiving combined therapy even though hypotension has rarely been noted with NIAMID alone. There has been no evidence of liver damage in patients on NIAMID; however, in patients who have any history of liver disease, the possibility of hepatic reactions should be kept in mind.

Dosage and Administration

Start with 75 mg. daily in single or divided doses. After a week or more, revise the daily dosage upward or downward, depending upon the response and tolerance in steps of one or one-half 25 mg. tablet. Once satisfactory response has been attained, the dosage of NIAMID may be reduced gradually to the maintenance level.

The therapeutic action of NIAMID is gradual, not immediate. Many patients respond within a few days, others satisfactorily in 7 to 14 days. Some patients, particularly chronically depressed or regressed psychotics, may need substantially higher dosages (as much as 200 mg. daily has been used) and prolonged administration before responses are achieved.

Supply

NIAMID is available in: 25 mg., pink, scored tablets and 100 mg., orange, scored tablets.

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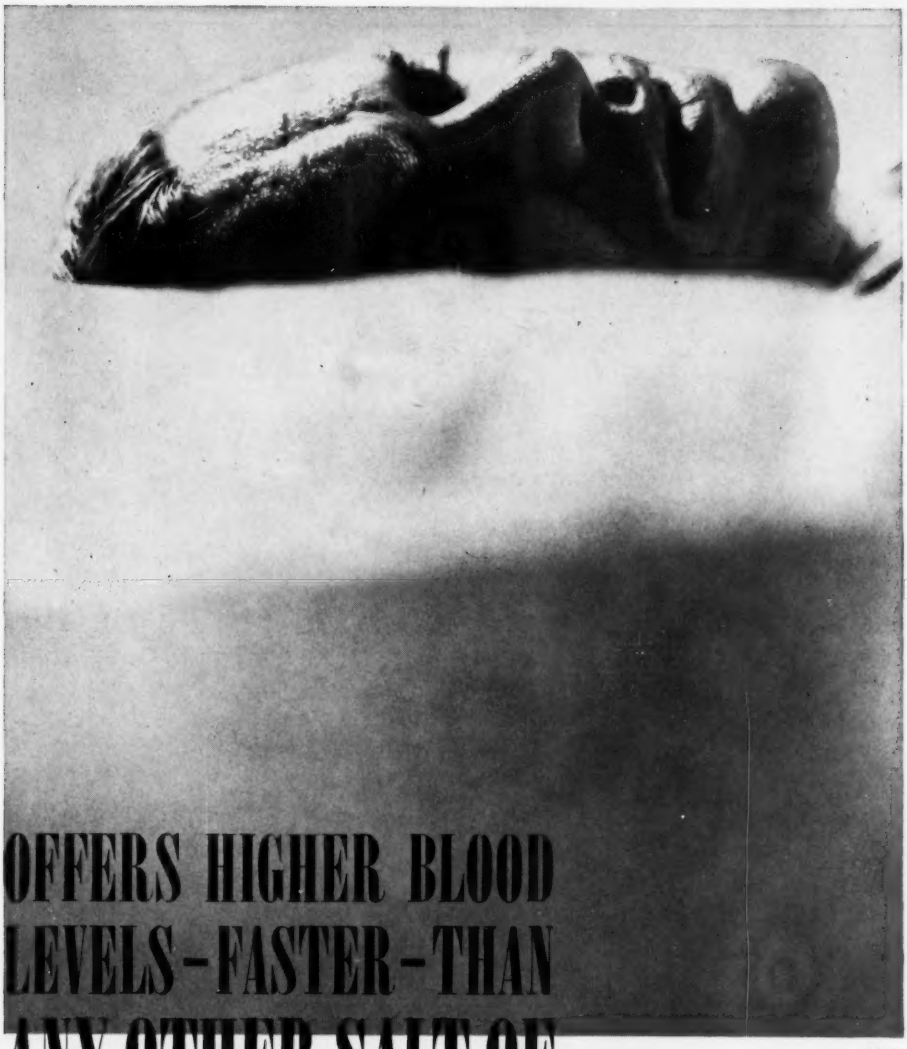

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